聲明

本檔案之內容僅供下載人自學或推廣化學教育之非營利目的使用。並請於使用時註明出處。[如本頁取材自○○○教授演講內容]。

Green Chemistry
綠色化學

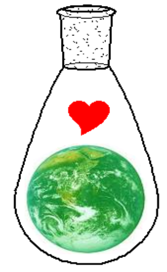
工業界綠色永續合成實例

Cases of Green, Sustainable Synthesis in Industrial World

第二次

2010 永續合成化學工作坊

May 7, 2010, 義守大學



朝陽科技大學　　周德璋

Green Chemistry

The design, development, and implementation of chemical products and processes to reduce or eliminate the use and generation of substances hazardous to human health and the environment.

［為縮減或淘汰對人類健康和環境具有危害性的物質的使用與產生，而進行化學產品和製造過程的設計、開發與執行。］

Anastas PT, Kirchhoff MM,
Origins, Current Status, and Future Challenges of Green Chemistry
Acc. Chem. Res. 2002, 35. 686.
Anastas PT, Warner JC, editors. *Green Chemistry: theory and practice.* Oxford: Oxford University Press; 1998.

（綠色化學的終極目的是縮減或淘汰對人類健康和環境具有危害性的物質的使用與產生，因此任何化學產品及其相關活動—製造過程的設計、開發、與實行，當然包含化學合成，都要秉持此認知而思考。）

The Twelve Principals of Green Chemistry

1. Prevent waste:
2. Design safer chemicals and products:
3. Design less hazardous chemical syntheses:
4. Use renewable feedstocks:
5. Use catalysts, not stoichiometric reagents:
6. Avoid chemical derivatives:
7. Maximize atom economy:
8. Use safer solvents and reaction conditions:
9. Increase energy efficiency:
10. Design chemicals and products to degrade after use:
11. Analyze in real time to prevent pollution:
12. Minimize the potential for accidents:

"Underlying the Green Chemistry approach is the recognition that all we have to work with on Earth is matter and energy."

［綠色化學方法之基礎是，認知到我們在地球上所能夠使用的，就是物質和能量。］

"Green Chemistry seeks to design and invent the next generation of matter (material) that is the basis of our society and our economy so that it minimizes adverse consequences to human health and the environment."

［綠色化學的目的是，設計和發明下一代我們的社會和經濟能夠賴以立基，並能夠對人類健康和環境有最小不利後果的物質（材料）。］

J. B. Manley, P. T. Anastas, B. W. Cue Jr.
Frontiers in Green Chemistry: meeting the grand challenges for sustainability in R&D and manufacturing,
J. Cleaner Production 16 (2008) 743.

Webster's definition of chemistry,
"the study of matter and all of its transformations."

Transformations are carried out by chemical synthesis.

"Synthetic chemistry in the 21th century is not just a great intellectual challenge, it is essential for addressing the many challenges that face humanity."# [**21** 世紀的合成化學並不只是一個重大的智力挑戰，有必要解決人類面臨的種種挑戰。]

Prof. Peter B. Dervan, California Institute of Technology,
2009 Welch Symposium on the Frontiers of Organic Synthesis

The most critical challenge is global sustainability.

“The challenges of global sustainability are most complex and definitionally the most consequential of any that civilization has or can encounter.”

“The three elements of sustainability, environmental, social, and economic must be recognized in the context shown in Fig. 1.”

“……., we must understand that the economy exists within society and the society exists within the environment.

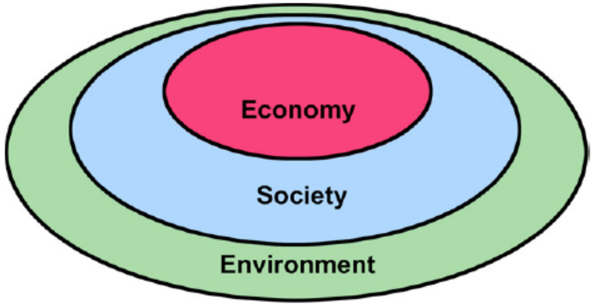


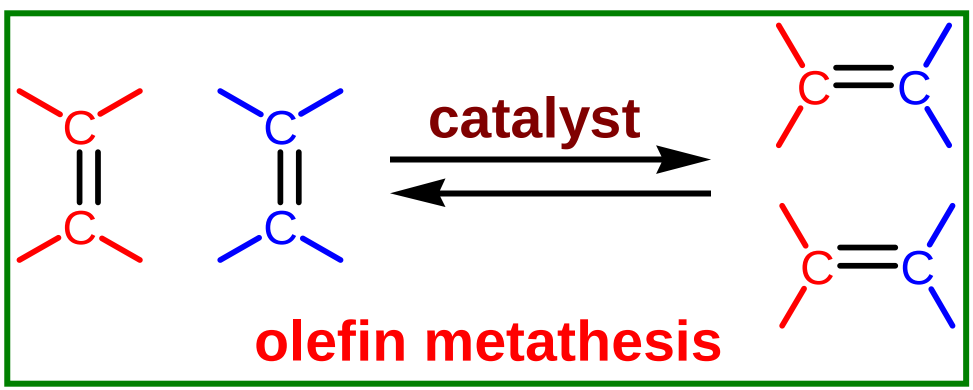
Fig. 1. A sustainable community [3].

“The true long-term goal must be to ensure that the goals of environment, society, and economy are working in concert in a synergistic way.” →→→ **Toward global sustainability.**

J. B. Manley, P. T. Anastas, B. W. Cue Jr. *J. Cleaner Production* 16 (2008) 743.

"Americans Robert H. Grubbs and Richard R. Schrock and France's Yves Chauvin won the 2005 Nobel Award for their development of the **metathesis** method in organic synthesis."

"This represents a great step forward for **green chemistry**, reducing potentially hazardous waste through smarter production. **Metathesis** is an example of how important basic science has been applied for the benefit of man, society and the environment,……"



What is the ideal synthesis

1. Convenient and practical -- Simple
2. High yield (100%!)
3. Short (1 step!)
4. Mild conditions (room temperature or 37 ^{o}C)
5. Starting materials easy to obtain (natural or commercial)
6. Available controlled stimulus (mild reagents or catalysts)
7. Cheap and safe solvent (water!)
8. Easy isolation of products
9. Isolation of intermediates unnecessary (one-pot reaction)
10. Display novel chemistry or new applications

As Mother Nature Does!


高
原子
效率
原料易取
簡便實用
綠色永續
合成
少步驟
(一步)
安全
節能
減廢
環境友善

Green Chemistry is focused on the design, manufacture, and the use of chemicals and chemical processes that have little or no pollution potential or environmental risk.

Sustainable Chemistry not only includes the concepts of green chemistry, but also expands the definition to a larger system than just the reaction. Also considers the effect of processing, materials, energy, and economics.

To process chemists

Process chemists and engineers in industry generally feel that green chemistry is an academic pursuit - until green chemistry considerations can lower the cost of goods. As Canales Clariond* said, "The world doesn't move because of idealism... It moves because of economic incentives."

<u>Editorial</u>: *Organic Process Research & Development* **2008,** *12,* 1019.

**Fernando Canales Clariond,*
former Mexican secretary of the economy:
steps new reactions and new technologies are important,
The Los Angeles Times, July 10, 2008:
http://articles.latimes.com/2008/jul/10/business/fi-seafarm10.

Lower the Cost of Goods (COG) and the Environment

- ✓ **Minimize waste**
  - ► Achieving higher yields
    reduces the environmental quotient (EQ) of waste production.
  - ► Processing using fewer unit operations and under more concentrated conditions
    reduce waste, cycle times, and labor costs.
- ✓ **Designing routes that require fewer steps**
  require smaller quantities of starting materials, solvents, and reagents and less labor; less waste and reduced costs for waste disposal.
- ✓ **Review and consider older approaches and replaced with new reactions and new technologies.**

- ✓ **Support new synthetic initiatives and encourage unbiased researchers from academia to invent new approaches to existing compounds.**
- ✓ **Provide feedback to drug discovery.**
  - ► **Is the most potent or bioavailable compound selected?**
  - ► **Can the compound be prepared in the fewest steps?**
  - ► **Is the chiral center of the prodrug really necessary?**
- ✓ **Selecting different starting materials through designing and redesigning routes to lower the COG .**

關心 COG

必能關心我們的環境

Twelve more principles of green chemistry

to all process chemists

(Winterton N, Green Chemistry 2001, G73)

1. **Identify and quantify byproducts**
   鑑定並定量所有的副產物
2. **Report conversions, selectivities and productivities**
   記錄所有的轉換率、選擇性和產量
3. **Establish full mass balance for process**
   建立製程中完整的質量平衡
4. **Measure catalyst and solvent losses in air and aqueous effluent**
   測量空氣和水的流出物中催化劑和溶劑的耗損量
5. **Investigate basic thermochemistry**
   查悉基本熱化學
6. **Anticipate heat and mass transfer limitations**
   預估傳熱與傳質的限制

Twelve more principles of green chemistry

7. **Consult a chemical or process engineer**
   諮詢化學或製程工程師
8. **Consider effect of overall process on choice of chemistry**
   考量整個製程對選擇化學的影響
   [化學反應和方法的選擇要依據整體製程]
9. **Help develop and apply sustainability measures**
   協助開發和應用永續發展的措施
10. **Quantify and minimize use of utilities**
    量化並減少使用通用性器材（水、電、煤氣等）
11. **Recognize where safety and waste minimization are incompatible**
    認知安全和廢棄物減化在（製程中）何處會是不相容的[不能兼顧的]
12. **Monitor, report and minimize laboratory waste emitted.**
    監控、記錄和減少實驗室的廢棄物排放

Material Efficiency:

The Concept of Atom Economy

Professor Barry M. Trost, Stanford University,
The winners of the *Academic Award* in
the US Presidential Green Chemistry Challenge Awards, 1998
for the Development of the Concept of Atom Economy

- **How many of the atoms of the reactant are incorporated into the final product and how many are wasted?**

[究竟有多少反應物的原子被合併到最終產 品，有多少被浪費？]

$$\text{\% Atom Economy} = \frac{\text{FW of atoms utilized}}{\text{FW of all reactants}} \times 100$$

Trost BM (1991)
The atom economy: A search for synthetic efficiency.
Science 254:1471–1477.

$$\text{Atom Economy} = \frac{\text{molecular wt. of desired product}}{\text{molecular wt. of all products}} \times 100\%$$

Chao-Jun Li and Barry M. Trost, *PNAS*, 2008, 105 (36), 13197–13202.

$$\text{Reaction Yield} = \frac{\text{quantity of product isolated}}{\text{theoretical quantity of product}} \times 100\%$$

The E Factor

[Environmental factor]

E-Factor = Total Waste (kg) / Product (kg)

（廢料總量/產物總量）

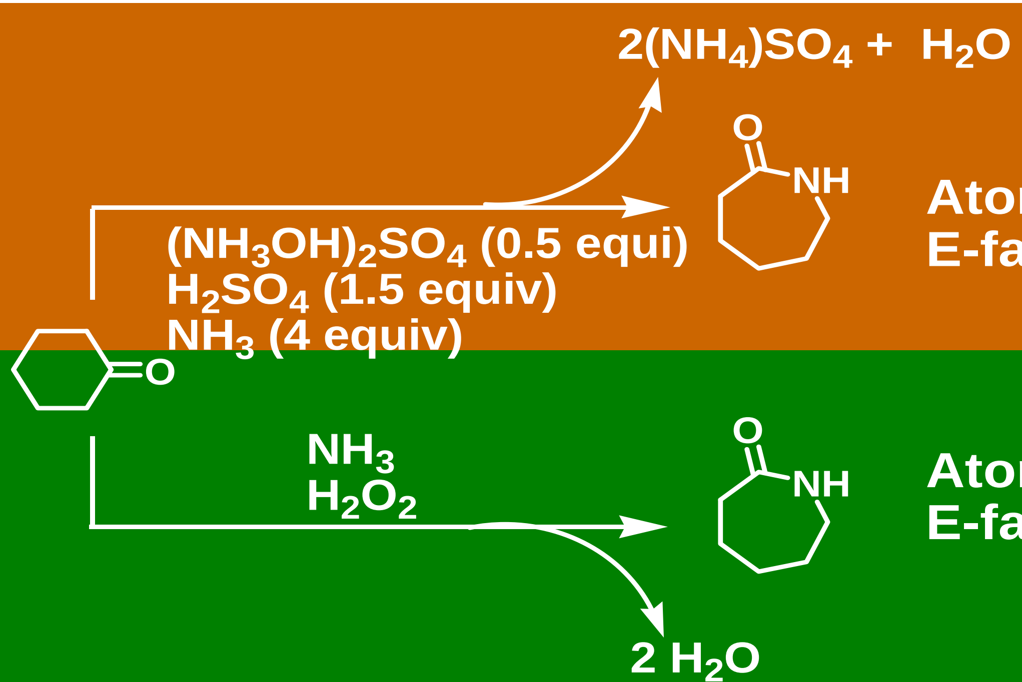
E-Factor = Raw materials-Product / Product (kg)

（原料總量−產物總量/產物總量）

Raw materials: substrate compounds, reagents, solvents, acid and base, catalyst, ….. and even materials for producing energy.
Products: target compounds (goods) and materials that are recovered.
Waste: Anything that enters and causes “burden” to the environment.

R.A. Sheldon, Chem & Ind,**1997**,12; **1992**,903

Industry segment	*Prodn(tons)*	*E-factor*
Oil refining	106–108	< 0.1
Bulk chemicals	104–106	<1–5
Fine chemicals	102–104	5–>50
Pharmaceuticals	10–103	25–>100



Atom Economy = 29%
E-factor = 2.5

Atom Economy = 75%
E-factor = 0.32

工業界綠色永續合成實例

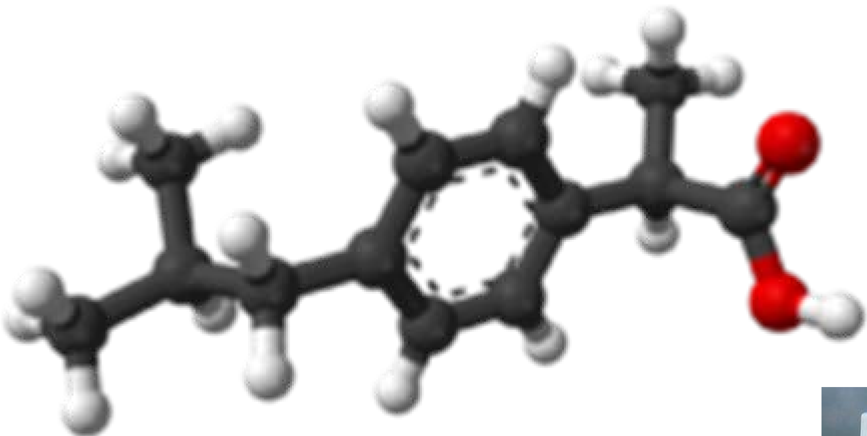
實例1. **Ibuprofen**

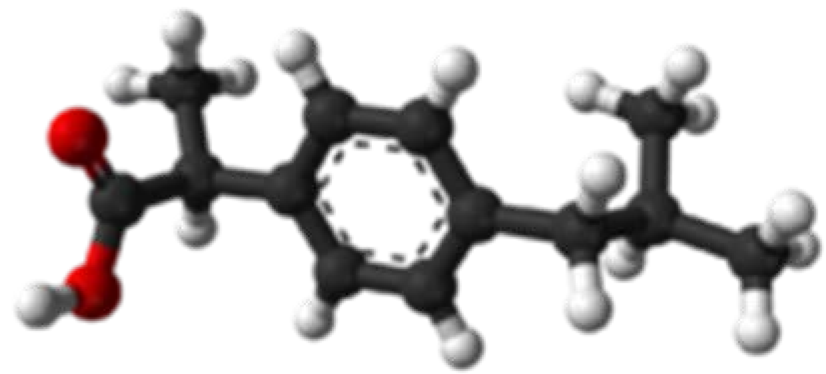
實例2. **Methyl Methacrylate (MMA)**

實例3. **Polyaspartate: Biodegradable Alternative to Polyacrylate**

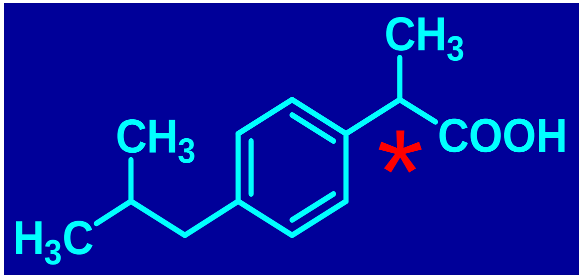
Case 1. 實例1

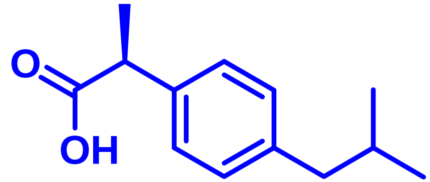
Ibuprofen



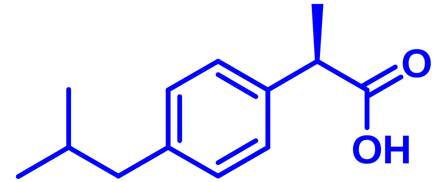


What is ibuprofen?





(S)-ibuprofen



(R)-ibuprofen

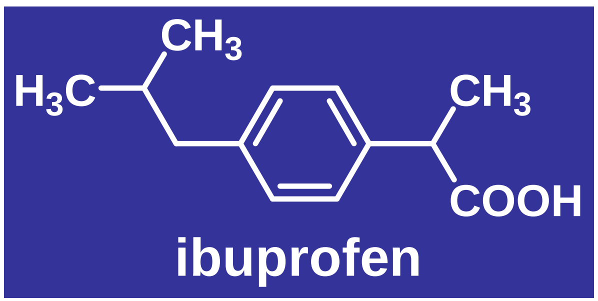
(S)-2-(4-isobutylphenyl)propanoic acid, (S)-ibuprofen, is active form both *in vitro* and *in vivo*.

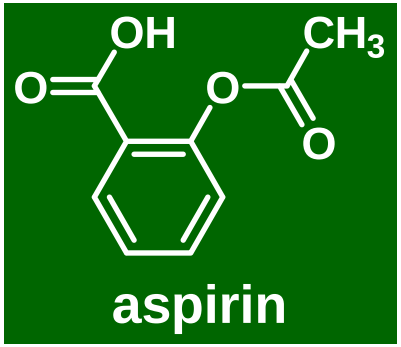
(S)-ibuprofen ← **(R)-ibuprofen**

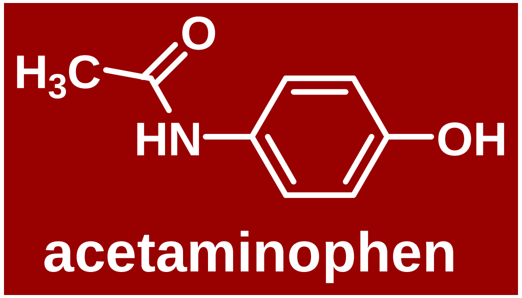
2-arylpropionyl-CoA epimerase (isomerase)

marketed as racemic mixtures.

- One of core non-steroidal anti-inflammatory medicines (非類固醇消炎藥) in the World Health Organization's "Essential Drugs List", which is a list of minimum medical needs for a basic health care system ---- *Over-the-Counter (不需處方可出售的) medicine.*
  [others: aspirin, paracetamol (acetaminophen)]







- Discovered by S. Adams, with J. Nicholson, A. R. M. Dunlop, J. B. Wilson & C. Burrows (Boots Company), and was patented in 1961. Dr. Adams initially tested the drug on a hangover（宿醉）.

- It was launched in 1969 as a medication for the treatment of rheumatoid arthritis [風濕性關節炎] in the UK and in 1974 in the USA.
- The Boots Group was awarded ***Queen's Award for Technical Achievement*** for the development of ibuprofen in 1987.
- 具解熱、消炎和鎮痛的作用，可治療發燒、疼痛和發炎。
- 減輕關節炎(arthritis) ，原發型痛經(primary dysmenorrhea)，發燒 (fever)，等症狀；作為止痛劑（analgesic)；具抑制血小板凝集效應（antiplatelet effect）。
- Active ingredient in “Motrin”, “Advil”, Medipren”….，“炎熱消”（水液），“普服芬”(錠劑), 宜痛炎錠, 伊普®鎮痛, ….

synthesis

- The industrial synthesis was developed and patented by Boots Company of England in 1961. ***--- brown synthesis***

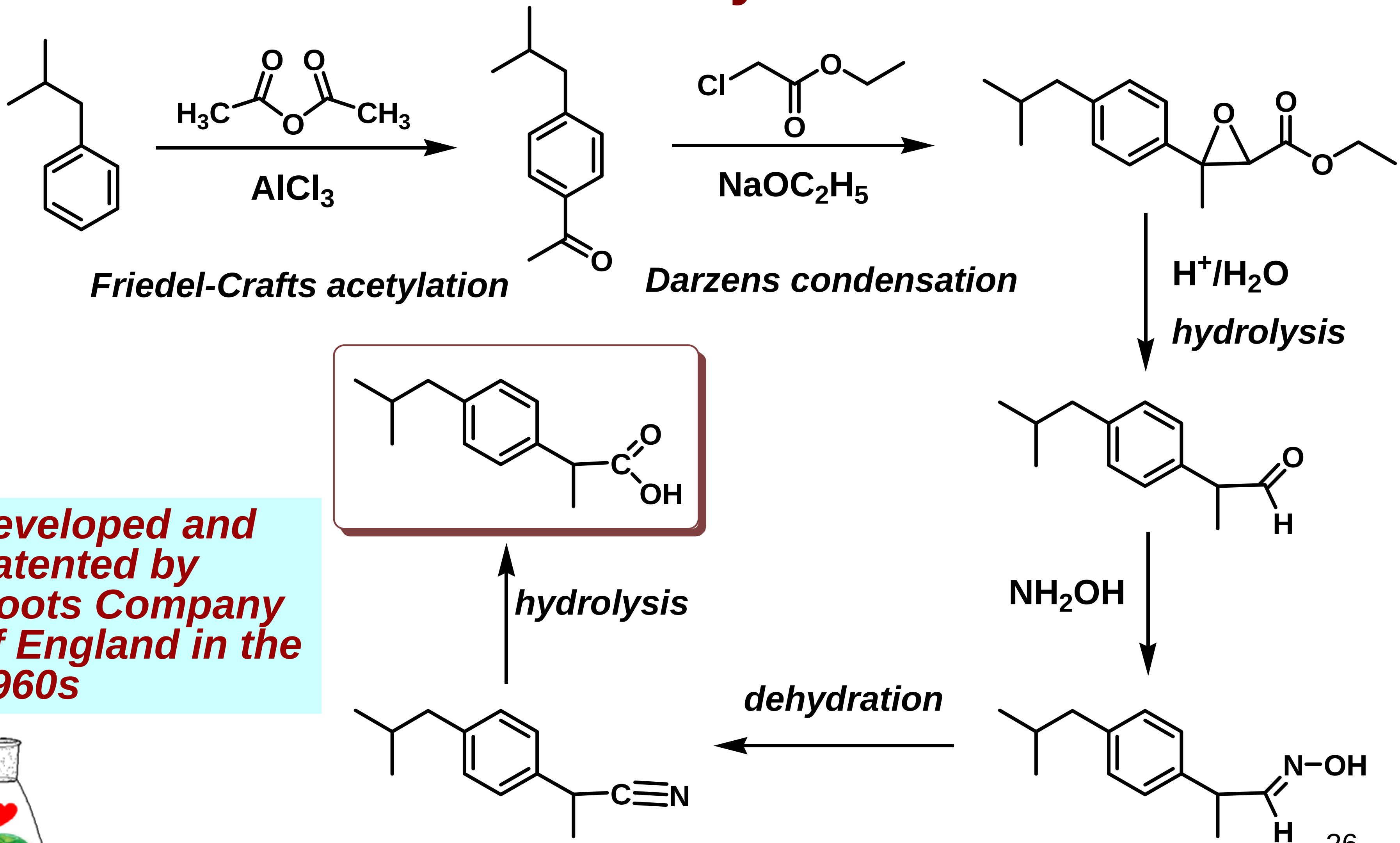
- A new greener industrial synthesis was developed and implemented by the BHC Company (now BASF Corporation) in 1991. ***--- green synthesis***

- BHC won Presidential Green Chemistry Challenge Awards (USA) **---- Greener Synthetic Pathways Award in 1997.**

BHC = Boots + Hoechst Celanese

Boots synthesis of ibuprofen

--- brown synthesis



developed and patented by Boots Company of England in the 1960s

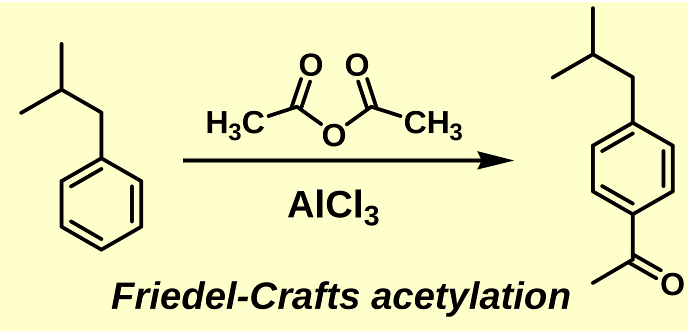
ibuprofen

	Reagent		Used in ibuprofen		Unused in ibuprofen	
	Formula	Mw	Formula	Mw	Formula	Mw
1	$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
	$C_4H_6O_3$	102	C_2H_3	24	$C_2H_3O_3$	75
2	$C_4H_7ClO_2$	122.5	CH	13	$C_3H_6ClO_2$	109.5
	C_2H_5ONa	68		0	C_2H_5ONa	68
3	H_3O	19		0	H_3O	19
4	NH_3O	33		0	NH_3O	33
6	H_4O_2	36	HO_2	33	H	3
	Total		Ibuprofen		Waste products	
	$C_{20}H_{42}NO_{10}ClNa$	514.5	$C_{13}H_{18}O_2$	206	$C_7H_{24}NO_8ClNa$	308.5

▸ = (206)/(514.5) x 100 = **40%**

Table 1. Atom economy in the Boots' synthesis of ibuprofen

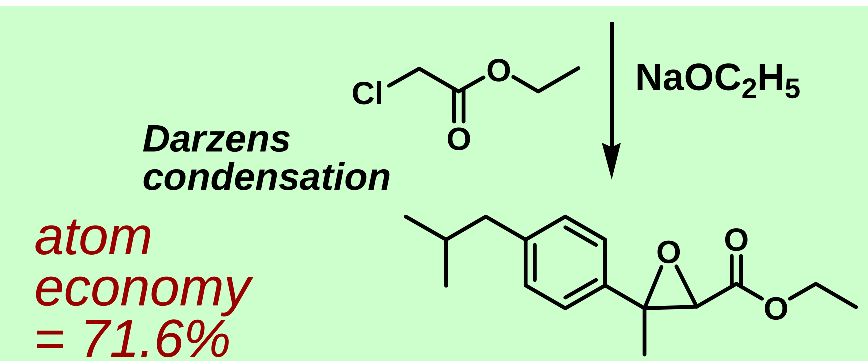
Problems with Boots synthesis of ibuprofen



atom economy = 74.5%

HCl AcOH Al

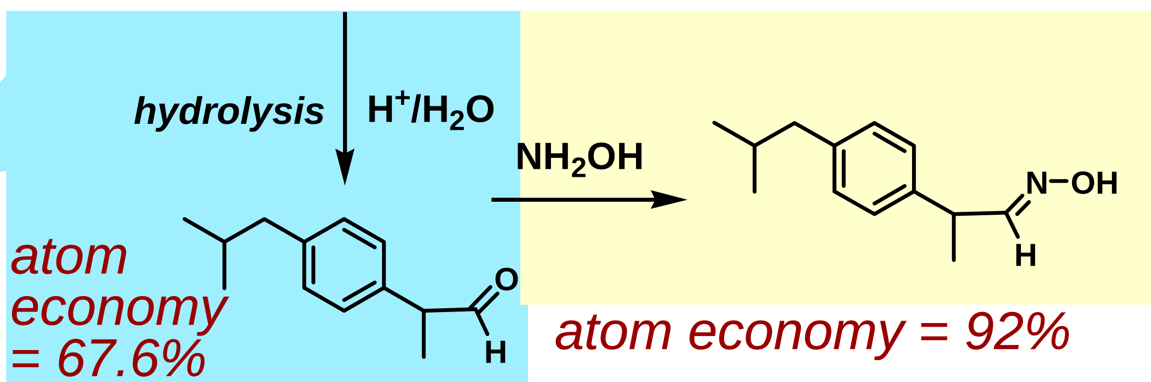
aluminium trichloride, $AlCl_3$, is not a true catalyst. it is changed into a hydrated form, $Al(OH)_3/H_2O$, that has to be disposed of – usually in landfill sites.



atom economy = 71.6%

NaCl C_2H_5OH

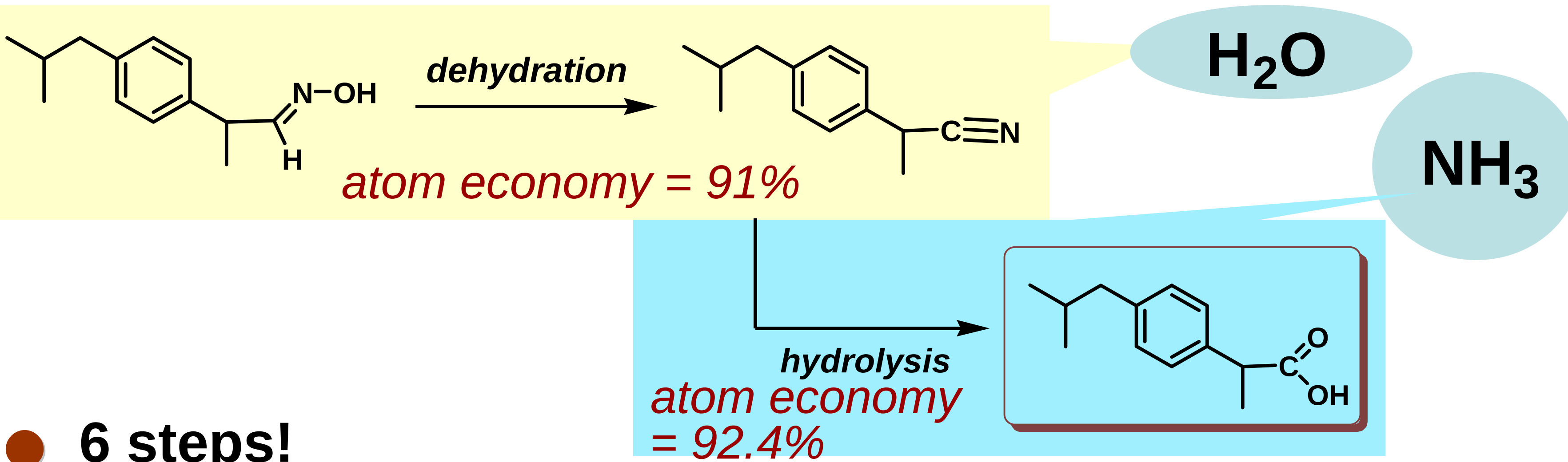
CO_2 C_2H_5OH



atom economy = 67.6%

H_2O

atom economy = 92%



- **6 steps!**

  If 90% yield for each step, then overall yield is 53%.

- **atom economy is 40%!**

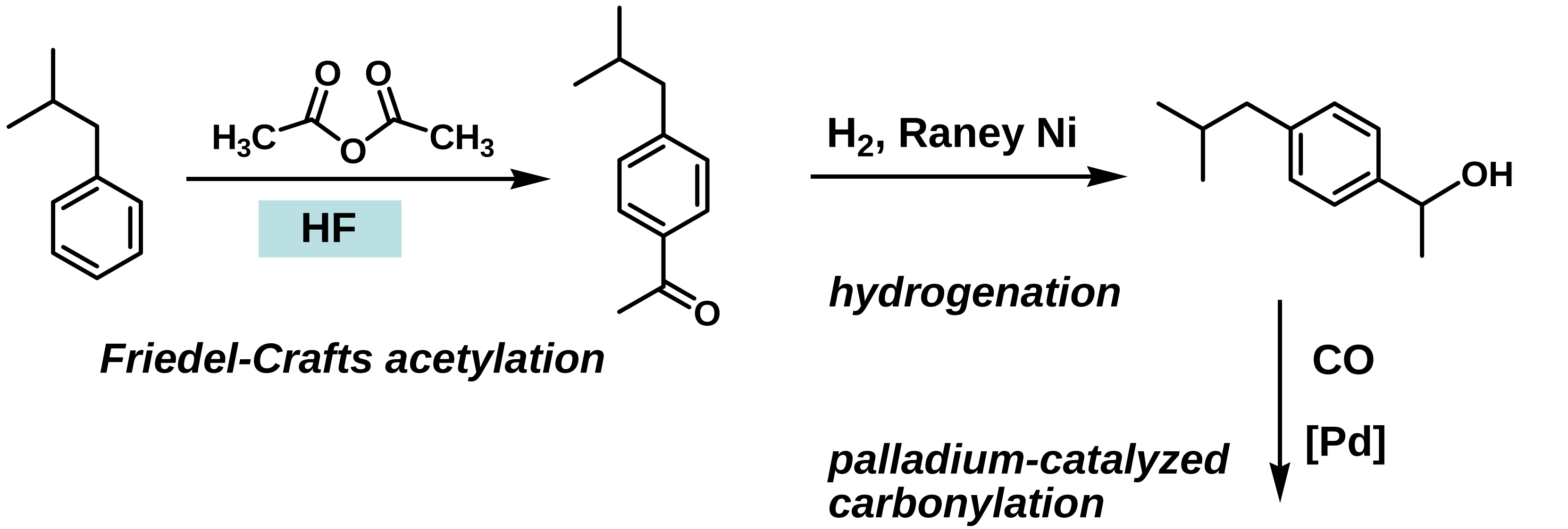
  thus every 1 kg of ibuprofen produced is accompanied with more than 1.5 kg of waste.

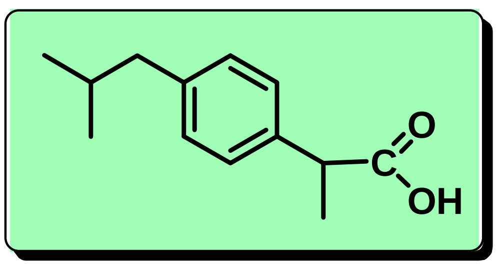
- **UK market for ibuprofen is about 3,000,000 kg per year!**
  - *about 4,500,000 kg of waste are produced.*
  - ***a typical tablet contains 200 mg of ibuprofen, then*** *15,000,000,000 (1.5×10^{10}) tablets are produced.*

BHC synthesis of ibuprofen
--- green synthesis

(USA) Presidential Green Chemistry Challenge Awards

Greener Synthetic Pathways Award in 1997

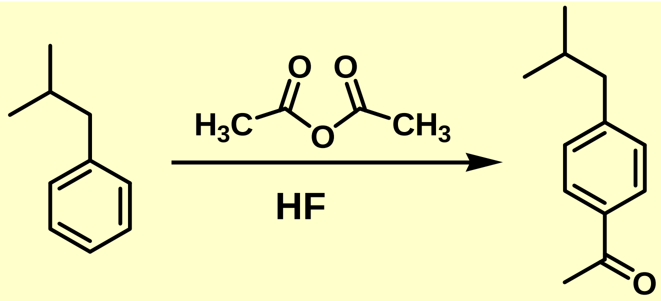




developed and implemented by the BHC Company in 1991

	Reagent		Used in ibuprofen		Unused in ibuprofen	
	Formula	**Mw**	**Formula**	**Mw**	**Formula**	**Mw**
1	$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
	$C_4H_6O_3$	102	C_2H_3O	43	$C_2H_3O_2$	59
2	H_2	2	H_2	2		0
3	CO	28	CO	28		0
	Total		**Ibuprofen**		**Waste products**	
	$C_{15}H_{22}O_4$	266	$C_{13}H_{18}O_2$	206	$C_2H_4O_2$	60
atom economy = (206)/(266) x 100 = **77.4%**						

Table 2. Atom economy in the BHC synthesis of ibuprofen

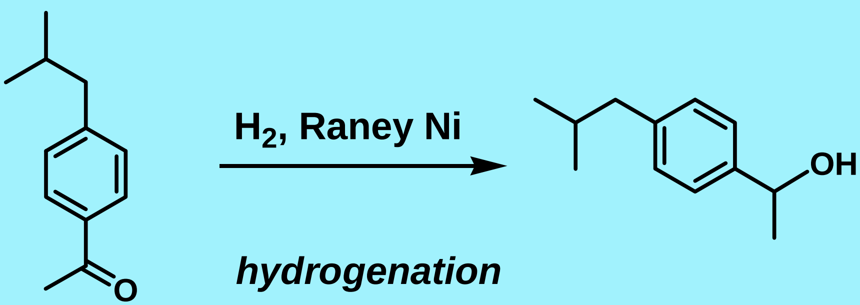


Friedel-Crafts acetylation

atom economy = 74.5%

HF AcOH

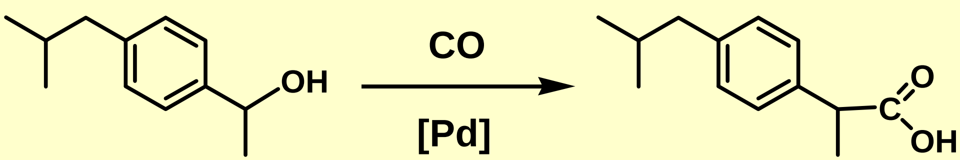
- Anhydrous hydrogen fluoride used as both catalyst and solvent ; it can be recovered (>99%) and reused.
- Acetic acid is recovered (>99%) and re-used.



hydrogenation

atom economy = 100%

- *Raney Ni is a spongy form of nickel made by dissolving the aluminium out of an Al-Ni alloy to leave holes.*



palladium-catalyzed carbonylation

atom economy = 100%

- Palladium is recovered and re-used.

Economic and Environmental Advantages of BHC Synthesis

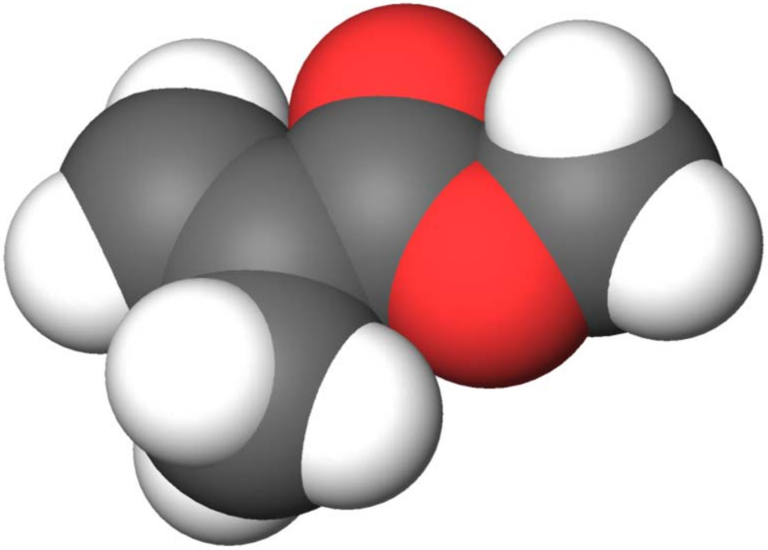
- Greater overall yield (three steps vs. six steps)
- Greater atom economy (uses less feedstocks)
- Fewer auxiliary substances (products and solvents separation agents)
- **Less waste:** greater atom economy, catalytic vs. stoichiometric reagents, recovery of byproducts and reagents, recycling, and reuse, lower disposal costs.

The BHC ibuprofen process is an innovative, efficient technology that has revolutionized bulk pharmaceutical manufacturing.

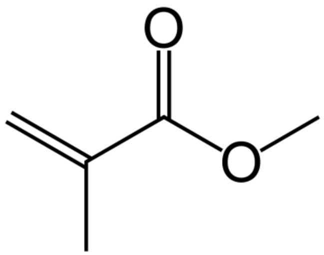
Case 2. 實例2

Methyl Methacrylate (MMA)

異丁烯酸酯，甲基丙烯酸酯



What is Methyl Methacrylate ?

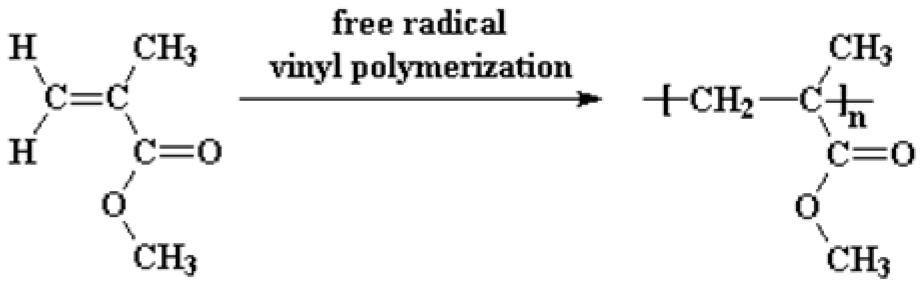
- 

  2-(methoxycarbonyl)-1-propene

Molecular formula	$C_5H_8O_2$
Molar mass	100.12 g/mol

  It is a colorless, volatile, flammable, liquid that is slightly soluble in water.

- It polymerizes readily upon heating in the presence of a free radical initiator to form polymethylmethacrylate (PMMA) resins.

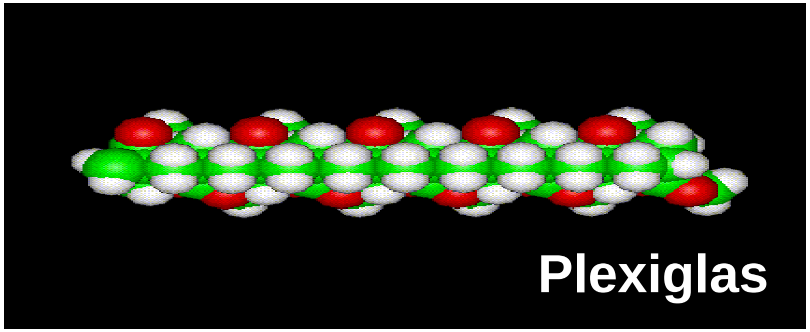


methyl methacrylate　　　poly(methyl methacrylate)

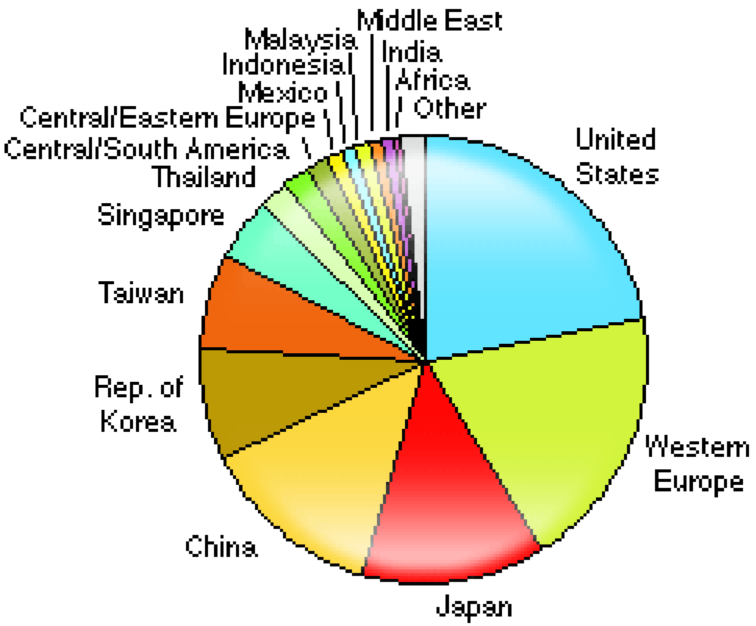
acrylates

acrylics

- PMMA resins is called “Plexiglass”, and sold by the names "Acrylite" and "Lucite" and is commonly called Acrylic Glass.
- MMA is also copolymerized with other monomers (vinyl acetate, acrylate esters or other methacrylates)
- Construction/remodeling activity, automotive applications and original equipment manufacture account for approximately 80% of world MMA consumption.
- The biggest emerging application of acrylics has been in Liguid Crystal Displays (LCD), demanded in Japan, South Korea, China, and Taiwan.
- At least 30 MMA manufacturing plants globally (2004) with a total capacity of about 2.5 million metric tons per year.



- **World Consumption of Methyl Methacrylate—2008**



Demand for MMA is greatly influenced by general economic conditions.

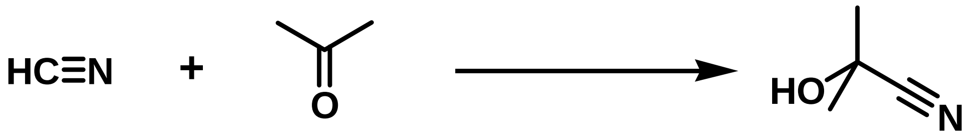
World consumption of MMA grew at an average annual rate of 3.6% during 2005–2008, down from 5.0% during 2002–2005, caused by a sluggish global economy.

S. Bizzari, **CEH Report :** June 2009.

- Most of the world's production of MMA is based on the route, pioneered in 1933 by ICI, that begins with hydrogen cyanide and acetone to make acetone cyanohydrin, and is known as the **ACH process**.

synthesis

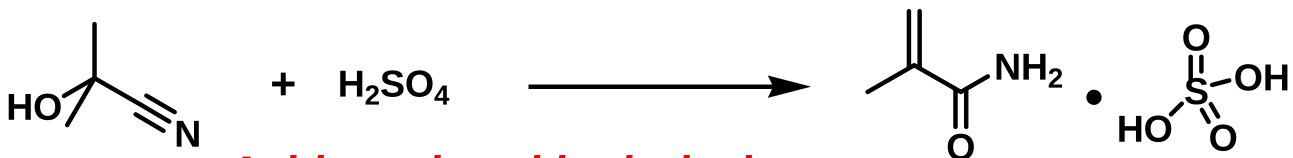
ACH Process --- brown synthesis



Nucleophilic addition

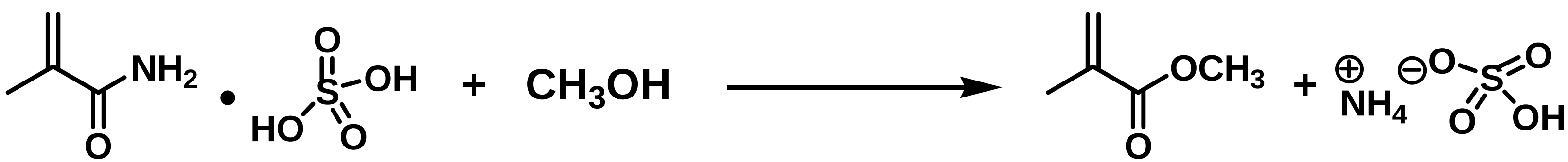
2-hydroxy-2-methylpropanenitrile
Acetone cyanohydrin (ACH)

Most popular route in the world's production of MMA, pioneered in 1933 by ICI.



Acid-catalyzed hydrolysis: hydration + dehydration

methacrylamide sulfate



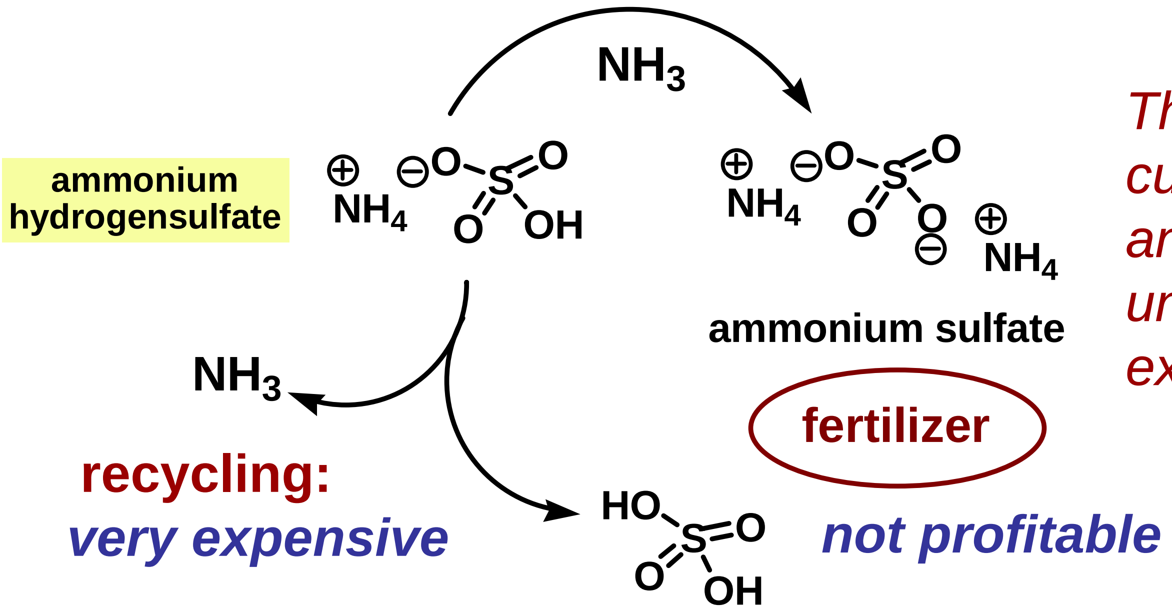
methacrylamide sulfate

Acyl substitution: esterification

% atom economy = [100／(27+58+32)]X100% = 85.5% (NH_3)

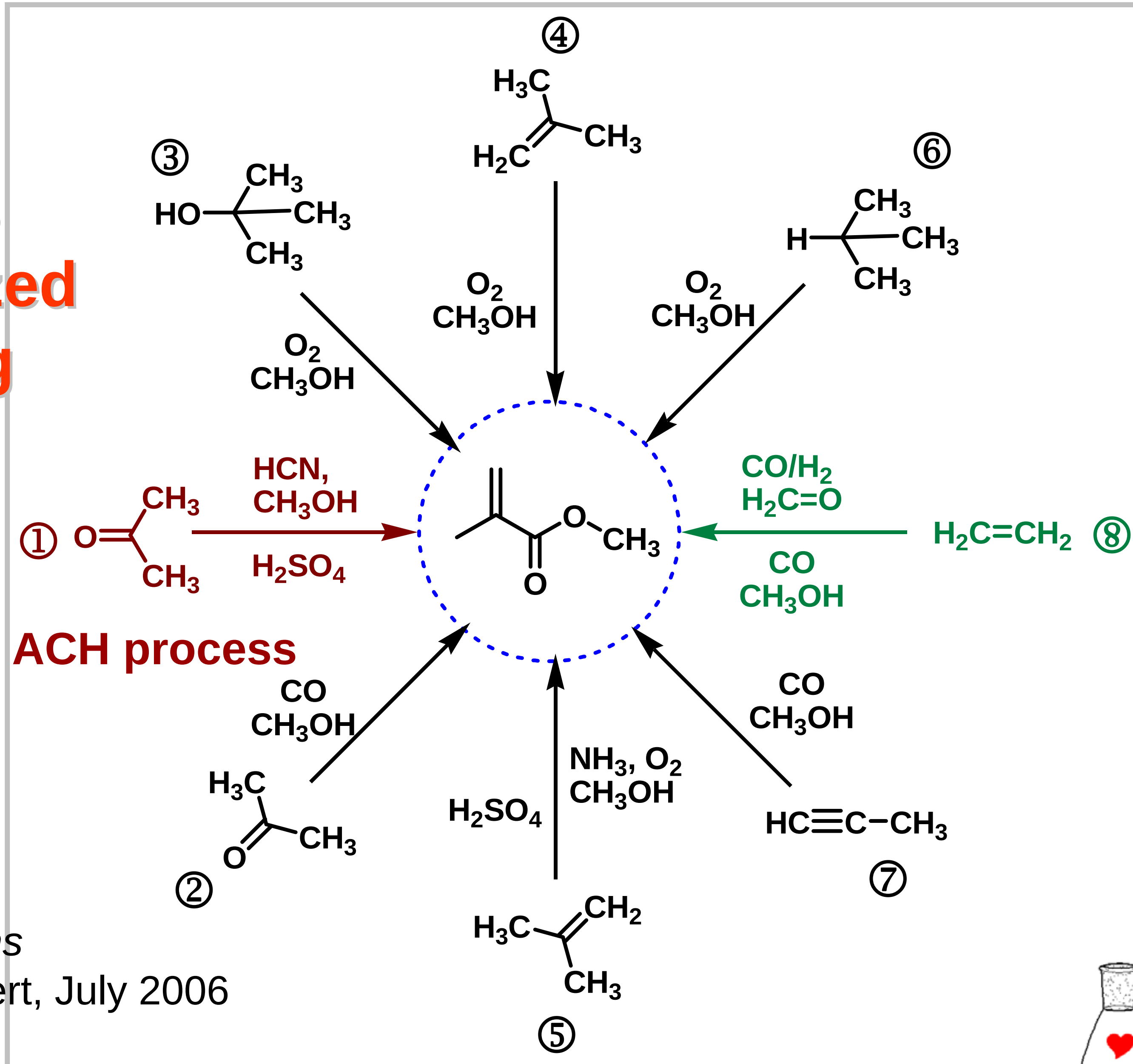
Problems with ACH Process

- **Hydrogen cyanide** (HCN): highly toxic, difficult sourcing,
- **NH_3 byproduct (atom lose)**
- **ammonium hydrogensulfate:**
  - *** about 1.2 tons/ton of MMA**
  - *** biggest pitfall to ACH process**



The ACH technology is currently environmentally and economically untenable for new expansions.

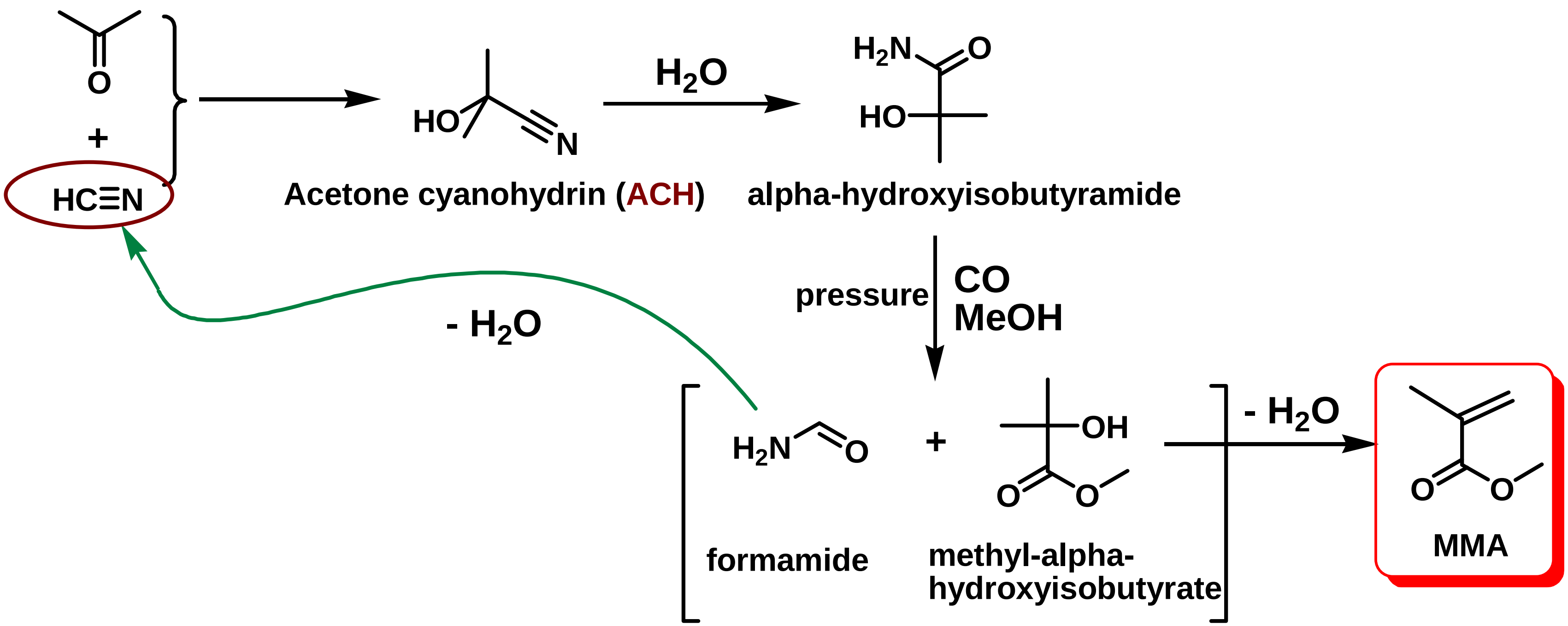
Major MMA Process Technologies Commercialized or Developing



Nexant's *ChemSystems*
PERP, New Report Alert, July 2006
http://www.nexant.com

① Most of the world's production of MMA is based on this route pioneered in 1933 by ICI, known as the **ACH process**. Mitsubishi Gas Chemicals developed a recycle version, in which ACH is made as usual from acetone and HCN. This process eliminates the expensive H_2SO_4 recovery plant.

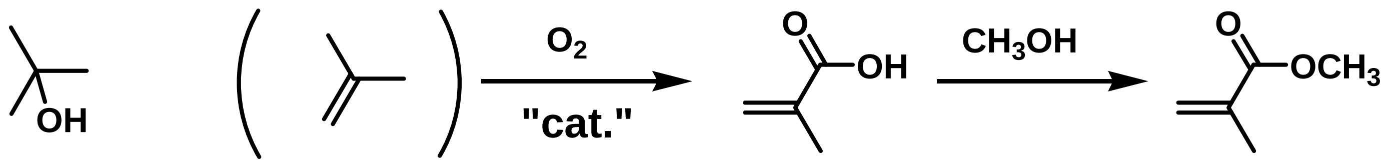
The “MGC” or Mitsubishi route:



③/④

The “i-C4”Route

Two-stage gas-phase oxidation of isobutylene (or TBA) to methacrylic acid, followed by esterification.

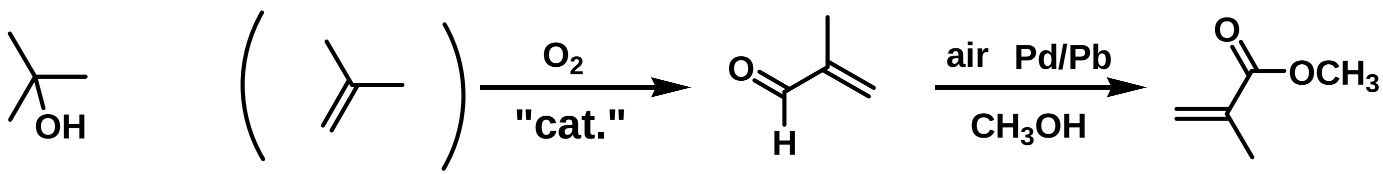


2-methylpropan-2-ol isobutylene methacrylic acid MMA

gas-phase oxidation *esterification*

The Asahi Chemical “Direct Metha” route

A new process in which isobutylene (or TBA) is first oxidized to methacrolein, which is then oxidized by air over a Pd/Pb catalyst with simultaneous esterification to MMA.



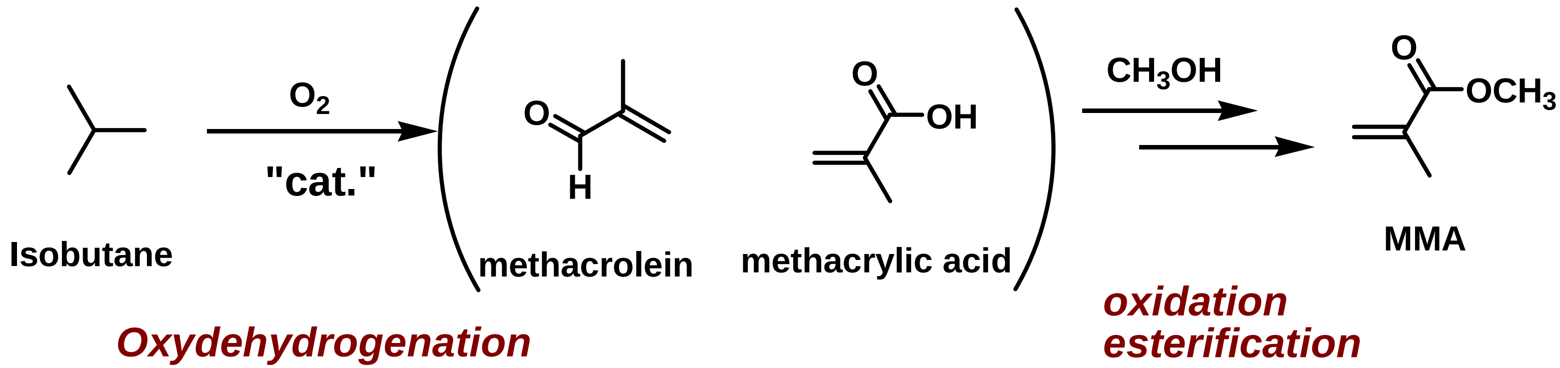
2-methylpropan-2-ol isobutylene methacrolein MMA

gas-phase oxidation *oxidation-esterification*

⑥ Isobutane Oxydehydrogenation to Methacrylein/Methacrylic acid:

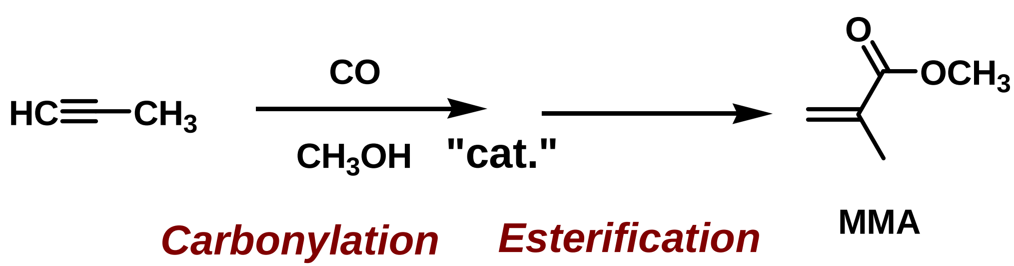
An analogous process to the established isobutylene selective oxidation. The most advanced is that of Arkema and Sumitomo.

Attraction: lower cost raw materials.



⑦ Carbonylation/Esterification of Propyne Directly to MMA:

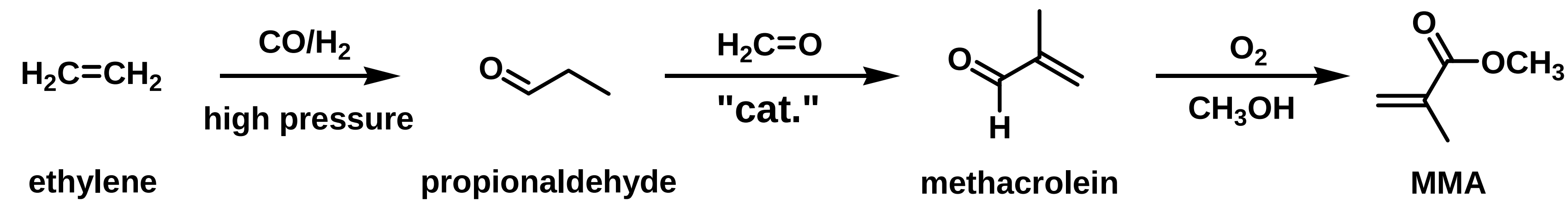
Developed by Shell. Very simple in concept. However, the availability of raw material is restricted.



⑧

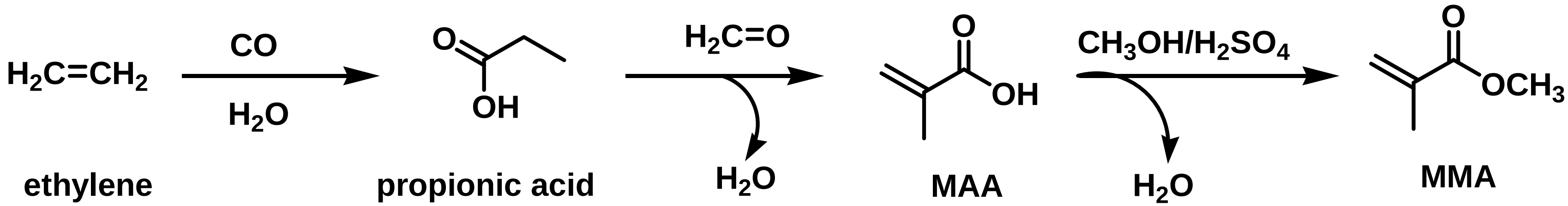
The BASF route

Hydroformylation of ethylene to propionaldehyde, condensation with formaldehyde to methacrolein, followed by oxidation and esterification.



Hydrocarbonylation ***condensation*** ***oxidation-esterification***

The RTI-Eastman-Bechtel Three-Step MMA process



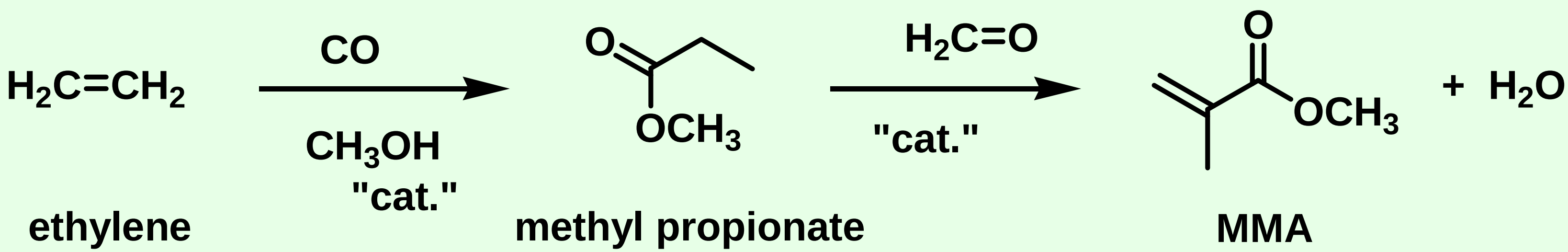
hydrocarbonylation ***condensation*** ***esterification***

__R__esearch __T__riangle __I__nstitute (RTI), __E__astman Chemical Company, and __B__echtel

⑧

The Alpha process

Combined carbonylation and esterification of ethylene to methyl propionate, which is reacted with formaldehyde under almost anhydrous conditions to form methyl methacrylate.



Hydrocarbonylation-esterification ***condensation***

% atom economy = [100／(28+28+30+32)]X100% = 84.7% (H_2O)

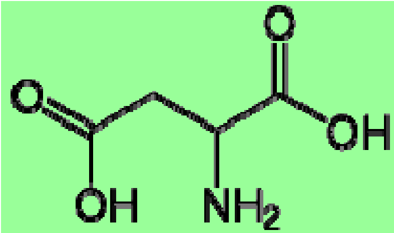
Developed by Lucite International, ICI's successor, and was acquired by Mitsubishi Rayon.

Lucite used this new technology for the first plant of 120,000 tons/year in Singapore (2008).

Case 3. 實例3

Polyaspartate

Biodegradable Alternative to Polyacrylate



Aspartic acid

天冬氨酸

2-Aminobutanedioic acid

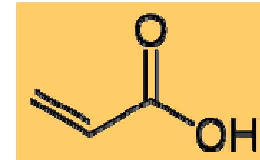
2-氨基丁酸

Acrylic acid

壓克力酸

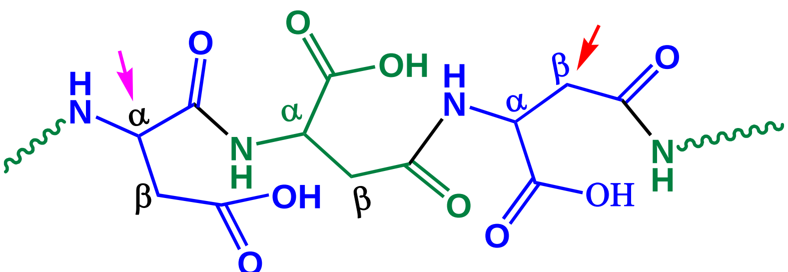
propenoic acid

丙烯酸



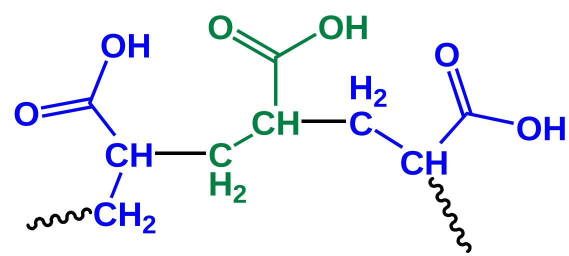
Polyaspartic acid

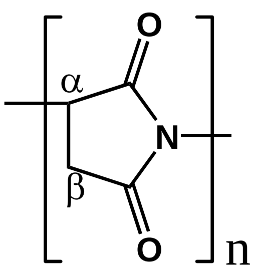
聚天冬氨酸



Polyacrylic acid

聚丙烯酸

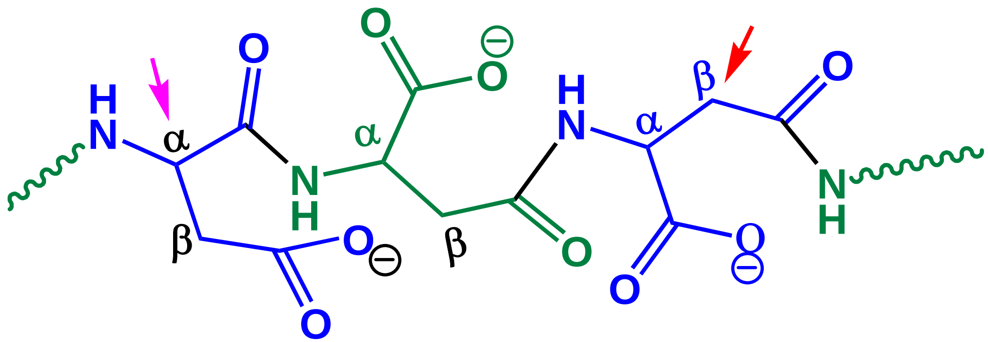




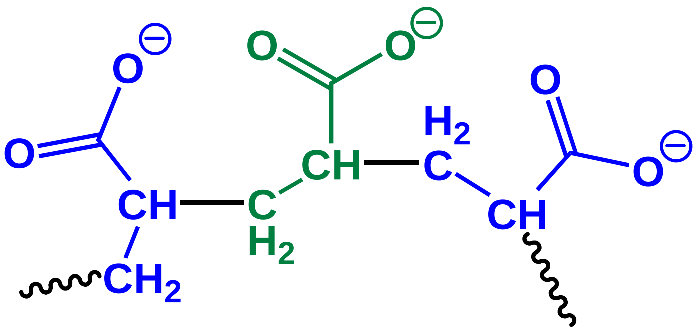
poly(succinimide)

Polyaspartate

Polyaspartate
聚天冬氨酸鹽

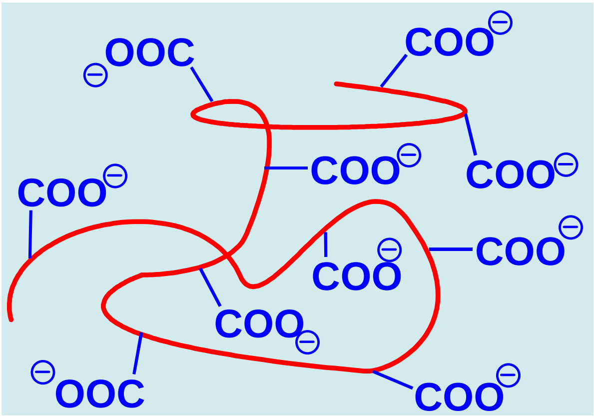


Polyacrylate
聚丙烯酸鹽



What are polyaspartate and polyacrylate in common?

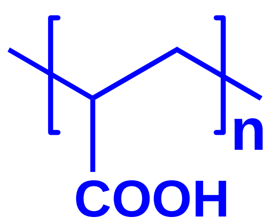
Polyanion, Hydrophilic, Water soluble



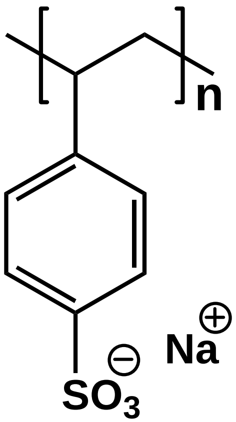
Polyelectrolytes

- polymers whose repeating units bear an electrolyte group, dissociating in aqueous solution (water) to generate positive or negative charge.
- also called macroions or polyions or polysalts.
- can be polyanions or polycations.
- generally water soluble polymers if their structure is linear.
- the polymer will be highly expanded in aqueous solution.

Examples

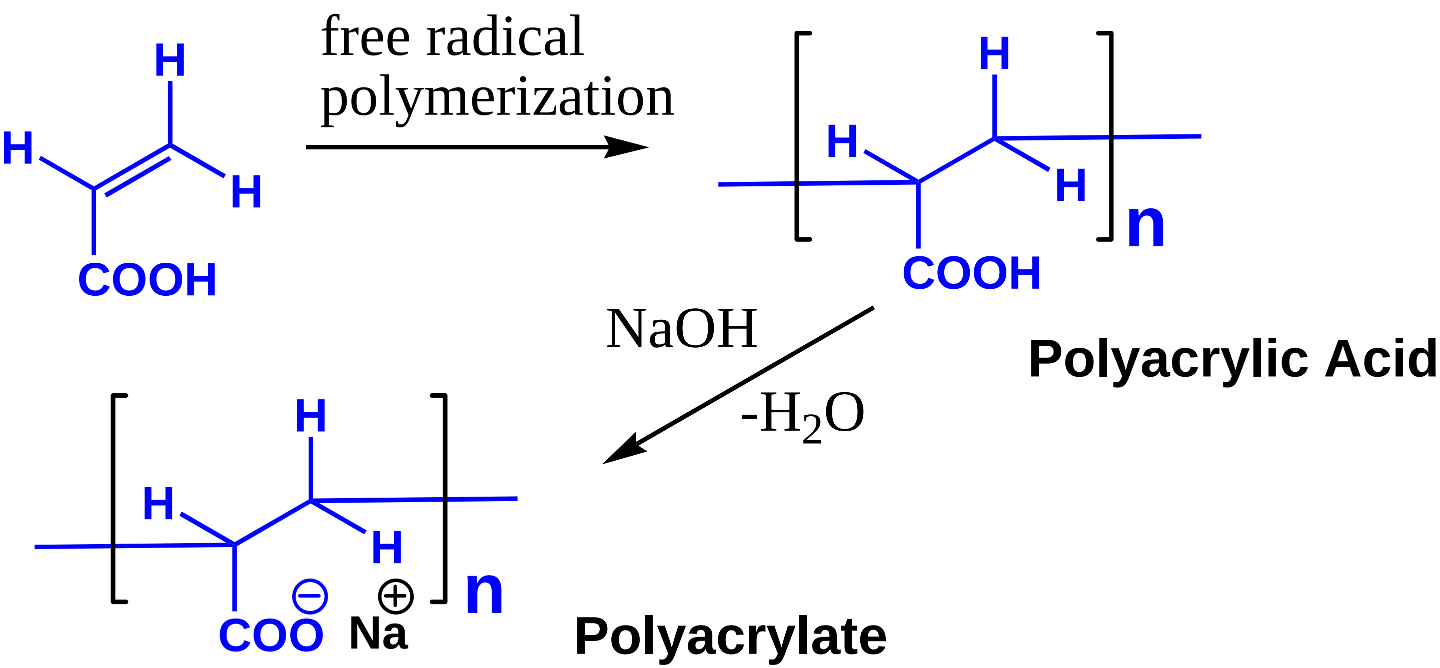


polypeptides (proteins), DNA, poly(sodium styrene sulfonate, PSS), polyacrylic acid (PAA).



Polyacrylate (PAC)

Synthesis



PAC can function as both
an antiscalant（抗垢劑 ）and a dispersant（分散劑）.

Antiscalants（抗垢劑 ）

- Prevent scale formation entirely or (完全防止結垢或)
- Permit the scale to be deposited in such a way that it is easily removed by the fluid flowing along the pipe or heat transfer surface. (使結垢能被沿著管道或熱傳送表面流動的流體輕易移除而清除。)
- Antiscalants complex with the cations present in water to prevent formation of the insoluble inorganic solids. (抗垢劑與水中陽離子錯合避免形成不溶性的無機固體顆粒。)

Scale *build up is a problem in industrial water handling processes because it results in reduced water flow though pipes, reduced heat transfer in boilers and condensers, and pump failures.*

Scale *consists of insoluble inorganic compounds such as calcium carbonate, calcium sulfate, and barium sulfate.*

Dispersants（分散劑）

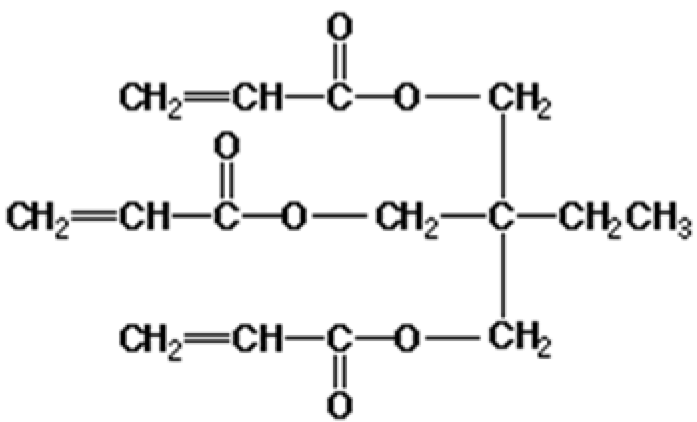
- Either a non-surface active polymer or a surface-active substance added to a suspension, usually a colloid, to improve the separation of particles and to prevent settling or clumping.（添加到懸浮體中，通常是一膠體，以改善顆粒的分離，防止其沈澱或凝集的非表面活性聚合物或表面活性物質。）
- Normally consist of one or more surfactants, but may also be gases.
- Can be found in lubricating oils, gasoline, concrete mix, detergents, oil drilling or spill, surface coating, process industry, cosmetics.....

PAC as an Antiscalant or Dispersant

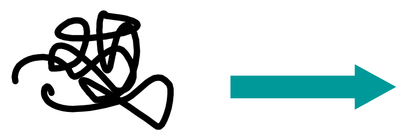
- Polymeric antiscalants are generally low molecular weight polymers.
- Polymeric dispersants consist of higher molecular weight fractions.
- Dispersants do not stop the formation of scale, but instead are able to keep the scale particles suspended in the bulk fluid by imparting a negative charge to the particles.
- Polyacrylate (PAC) is one of the most common scale inhibitors.
- PAC comprises 5% of many laundry detergent formulations because of its dispersant properties.

現在，全世界每年大約使用2億3000萬公斤的聚丙烯酸類，添加於洗衣劑之中。

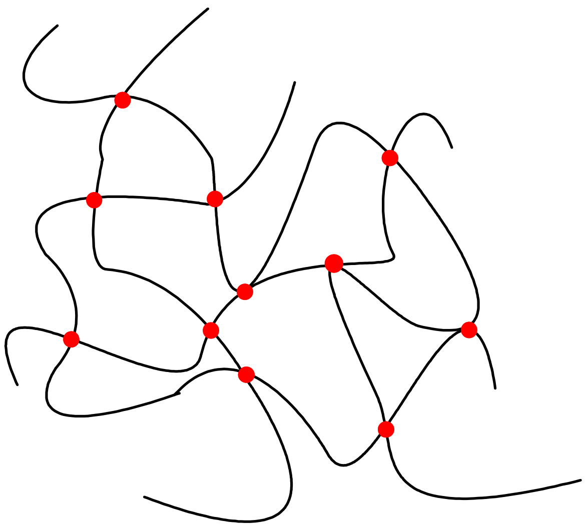
- A crosslinked form of the sodium salt of polyacrylic acid is used as a superabsorbant material in diapers and other personal hygiene products.
- Crosslinked PAC has a great affinity for water, but is unable to dissolve and will instead swell in aqueous solution.



Crosslinking Agent



Dry Crosslinked Polymer



Swollen **Crosslinked Polymer**

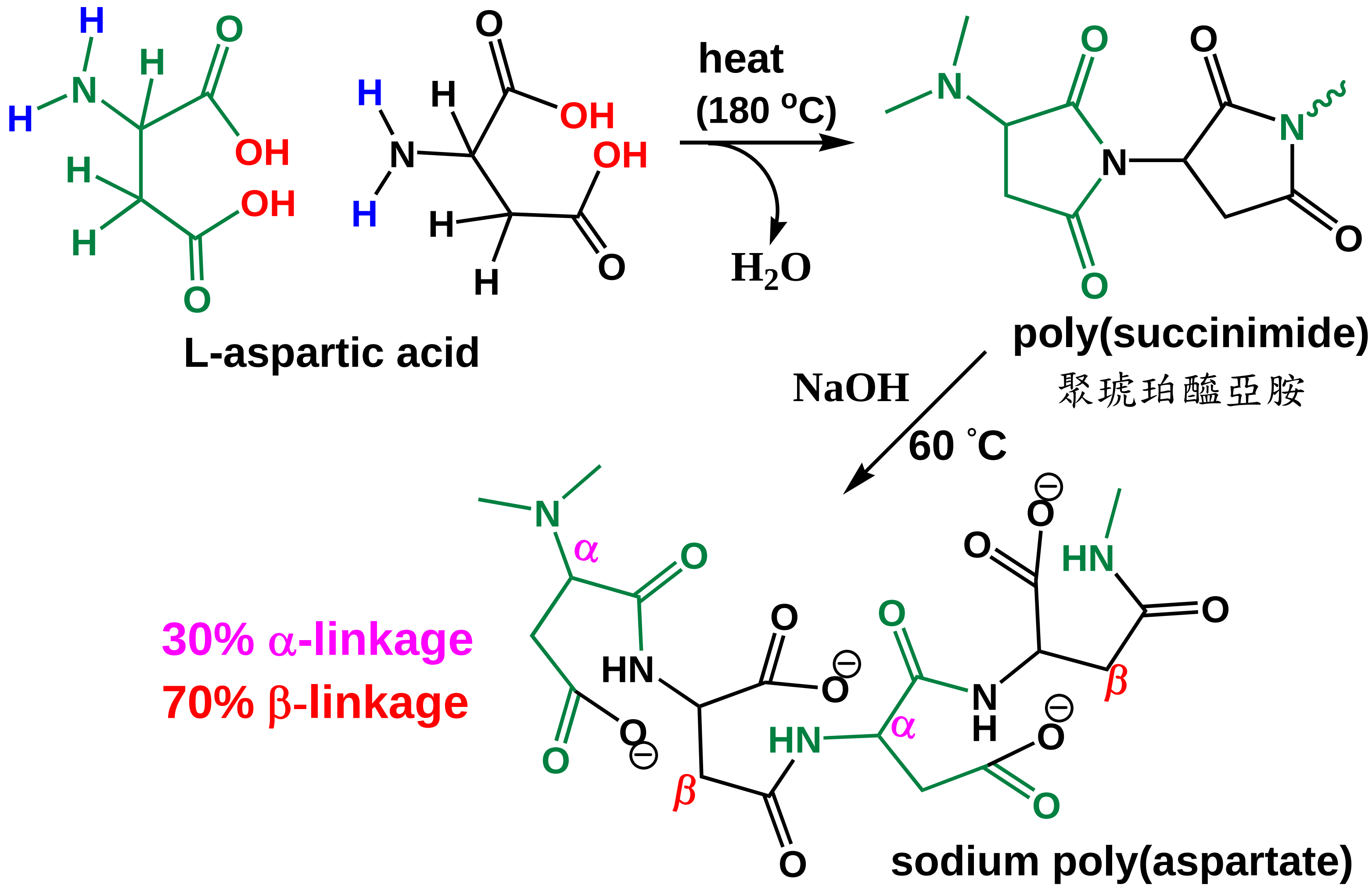
PAC and the Environment

- PAC is nontoxic and environmentally benign, but it is not biodegradable.
- Because it is widely used for many applications, it poses an environmental problem from a landfill perspective.
- When PAC is used as an antiscalant or a dispersant, it becomes part of wastewater.
- PAC is nonvolatile and not biodegradable, so the only way to remove it from the water is to precipitate it as an insoluble sludge.
- The sludge must then be landfilled.
- Feedstocks are made from fossil fuels.

Polyaspartate

- Polyaspartate has similar properties to the polyacrylates and so it can be used as a dispersant, or an antiscalant, or a superabsorber.
- Polyaspartate is nontoxic, biodegradeable（可生物分解的）, and environmentally safe.
- Biodegradation results in decomposition of TPA to environmentally benign products such as carbon dioxide and water.
- The Donlar Corporation developed an economic way to produce “thermal polyaspartate (TPA)” in high yield (~97%), that eliminates use of organic solvents, cuts waste, and uses less energy.
- Polyaspartate is a biopolymer synthesized from L-aspartic acid, a natural amino acid.

Synthesis of thermal polyaspartate (TPA)



30% α-linkage
70% β-linkage

Green Chemistry *in ACTION*

- In April 1997, Donlar opened the world's largest manufacturing facility for biodegradable polyaspartates, in Peru, Illinois, with a production capacity of more than 30 million pounds a year.
- The opening of this facility resulted in commercial availability of TPA.
- TPA is marketed and sold as a corrosion and scale inhibitor, a dispersing agent, a waste water additive, a superabsorber, and also as an agricultural polymer.
- As an agricultural polymer, TPA is used to enhance fertilizer uptake by plants. Less fertilizer is added to the soil and the environmental impact from fertilizer run-off is reduced.

- British Petroleum Exploration and others have achieved success with a TPA additive that helps to sustain the flow of crude from oil wells in North Sea offshore oil fields.

TPA is a green alternative to Polyacrylate and other currently used water soluble polymers!

Donlar Corporation

- A small company founded in 1990 that is committed to producing environmentally friendlier products.
- Spent the next five years and $50 million developing the chemistry and the process technology for polyaspartates to offer competitive market pricing.
- **Received the first Presidential Green Chemistry Challenge Award in the small business category in 1996.**
- Donlar has received several U.S. and foreign patents for the manufacture, composition and end use of their bioenvironmental technology.
- The company as a whole did $6.4 million in sales in 2000.

Pietrangelo: “It's a funny thing about being environmentally friendly: everybody's in favor of it, but nobody wants to pay more for it.”
(皮坦戈婁說：「環保的可笑之處在於，每個人都贊成，但沒有人願意為它多花點錢。」)

**皮坦戈婁: 資深化工經理、現任唐拉生化公司營運長*

Koskan agrees: “Though TPA is a tremendous technology, we had to forget about its green chemistry aspects and go with the idea that we‘ve got a novel product that is competitive based on its merits.” (柯斯康也同意這樣的看法：「雖然TPA是一項很棒的科技，我們卻必須忘記它綠色化學的一面，而得要把它想成，我們擁有一個其優點具有市場競爭力的新產品。」) **柯斯康唐拉持的創辦人*

If Donlar can show continued success, it may help revive an environmental chemistry sector saddled with a reputation for ineffectiveness and high cost. And, as a profitable venture, it may finally lend an additional meaning to the “green” in green chemistry.

(如果唐拉持續有進展，也許能夠幫助環境化學領域從「無效又昂貴」的臭名中鹹魚翻身。再者，身為一個營利企業，也許它最終可為綠色化學增添「綠意盎然」的新意。）

References

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2. Wood, A. ***"Acrylics: Versatile Chemistry Adapts to Growth Market Emulsions and Superabsorbents Take the Lead",*** *Chemical Week,* **1994,** (Dec 22), 22.

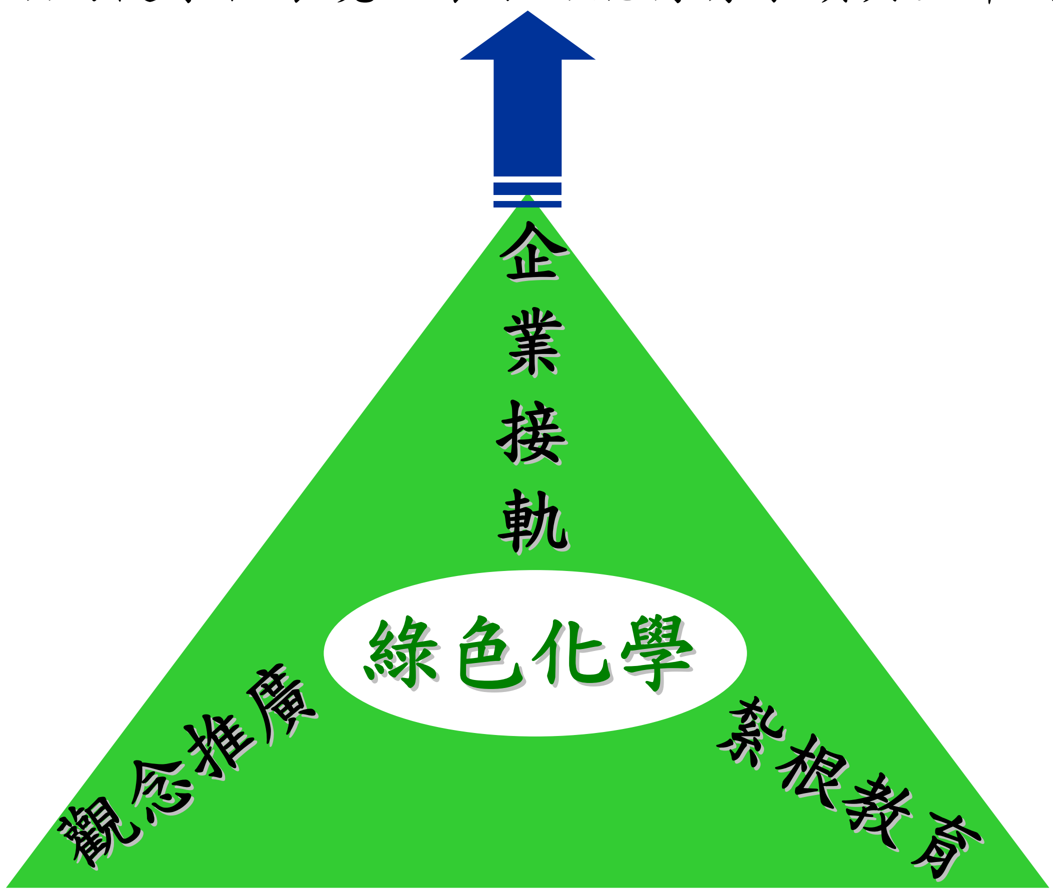
3. Wheeler, A.P., Koskan, L.P. ***"Large Scale Thermally Synthesized Polyaspartate as a Substitute in Polymer Applications",*** *Mat. Res. Soc. Symp. Proc.,* **1993,** *292,* 277.

4. R. A. Gross and B. Kalra, ***“Biodegradable Polymers for the Environment”,*** *SCIENCE* VOL 297 2 AUGUST 2002, 803, www.sciencemag.org

Sustainability

“safeguarding human health and environment to allow for future generations to maintain the necessary resources to sustain life”

［**永續性：**守護人類的健康和環境，讓子孫能持有永續其生命的必需資源。］



“The chemical industry plays a key role in sustaining the world economy and underpinning future technologies, yet is under unprecedented pressure from the effects of globalization and change in many of its traditional markets.”

［化學工業在永續世界經濟和奠立未來的技術上扮演著關鍵的角色，但也承受著來自全球化和很多傳統市場變化的衝擊所帶來的前所未有壓力。］

“Against this background, what will be needed for the industry to embrace efforts to make it "greener"?”

［在這種情況下，工業界致力於成為“更綠色”的努力中，會需要些什麼？］

Green Chemistry: Science and Politics of Change,
M. Poliakoff, J. M. Fitzpatrick, T. R. Farren, P. T. Anastas,
Science, **2002**, 297, 807 – 810.

感謝您的聆聽，請指教

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tcchou@cyut.edu.tw

附錄一 (p.66~70)

The Twelve Principals of Green Chemistry

Originally published by Paul Anastas and John Warner in
Green Chemistry: Theory and Practice
Oxford University Press: New York, 1998.

The Twelve Principals of Green Chemistry

1. **Prevent waste:**

   Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.

   ［防止廢棄物： 設計化學合成，以防止廢棄物產生，就不必處理或清理廢棄物。］

2. **Design safer chemicals and products:**

   Design chemical products to be fully effective, yet have little or no toxicity.

   ［設計更安全的化學品及產品：設計完全有效，但有很少或沒有毒性的化學產品。］

3. **Design less hazardous chemical syntheses:**

   Design syntheses to use and generate substances with little or no toxicity to humans and the environment.

   ［設計危害性較小的化學合成： 設計使用及與生產對人類及環境很少或沒有毒性的物質之的合成。］

4. **Use renewable feedstocks:** ***Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.***

   ［使用可再生原料：使用可以再生的而不是消耗性的原料。 可再生原料通常由農產品或其他製程的廢物；消耗性原料是由化石燃料（石油、天然氣的氣或煤），或採礦獲致。］

5. **Use catalysts, not stoichiometric reagents:** ***Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.***

   ［使用催化劑，不是計量試劑：使用催化反應以減少廢物。催化劑使用量少，並可 多次使用於單一反應。它們比過量及僅一次使用的化學計量試劑來得好。］

6. **Avoid chemical derivatives:** ***Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.***

   ［避免化學物的衍生： 盡可能避免使用阻檔或保護基或任何暫時需要的修改。衍生化使用附加的試劑並產生廢物。 ］

7. **Maximize atom economy:** ***Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.***

[最大化原子經濟： 設計最終產品包含最大部分起始材料的合成。浪費的原子應該很少，如果有的話。]

8. **Use safer solvents and reaction conditions:** ***Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.***

[使用更安全的溶劑及反應條件： 避免使用溶劑、 分離劑或其它輔助的化學品。如果需要這些化學物質，使用無毒無害的化學物質。]

9. **Increase energy efficiency:** ***Run chemical reactions at ambient temperature and pressure whenever possible.***

[提高能源效率： 盡可能在室溫和壓力下執行化學反應。]

10. **Design chemicals and products to degrade after use:** ***Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.***

[設計使用後可降解的化學品和產品： 設計使用後可分解為無害物質的化學產品，使他們不會在環境中積累。]

11. Analyze in real time to prevent pollution: Include *in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.*

［即時分析防止污染： 在合成過程中，納入即時監測與控制， 使副產物的形成最小化或消除。 ］

12. Minimize the potential for accidents: *Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.*

［最小化潛在的意外： 設計能夠儘量減少潛在化學事故 （包括爆炸、火災、及釋出到環境）的化學品及其形態（固體、 液體或氣體）。 ］

附錄二 (p.71~76)
Atom Economy

Trost BM (1991) *The atom economy: A search for synthetic efficiency. Science* 254:1471–1477.

Chao-Jun Li and Barry M. Trost, *PNAS*, 2008, 105 (36), 13197–13202.

How many of the atoms of the reactant are incorporated into the final product and how many are wasted?

[究竟有多少反應物的原子被合併到最終產 品，有多少被浪費？]

$$\text{\% Atom Economy} = \frac{\text{FW of atoms utilized}}{\text{FW of all reactants}} \times 100$$

$$\text{Atom Economy} = \frac{\text{molecular wt. of desired product}}{\text{molecular wt. of all products}} \times 100\%$$

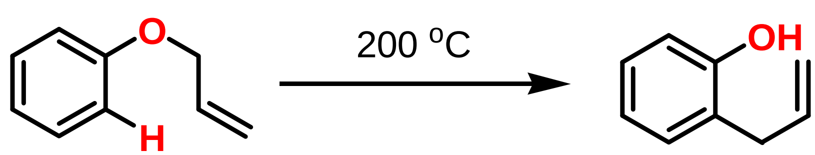
$$\text{Reaction Yield} = \frac{\text{quantity of product isolated}}{\text{theoretical quantity of product}} \times 100\%$$

Examples

- ***Isomerization***

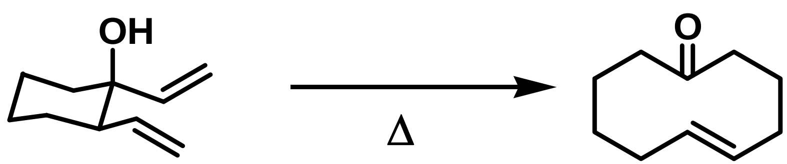
% atom economy = 100%

Claisen Rearrangement

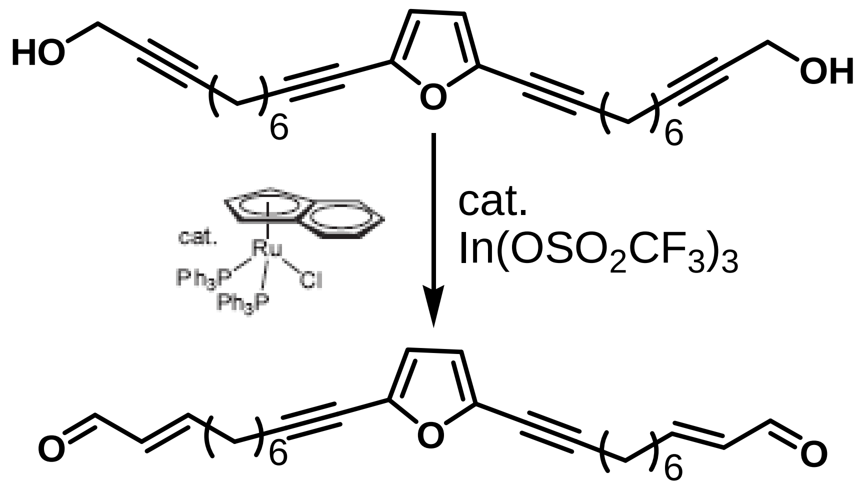


% atom economy = (134.18/134.18) x 100% = 100%

Oxy-Cope Rearrangement



% atom economy = 100%

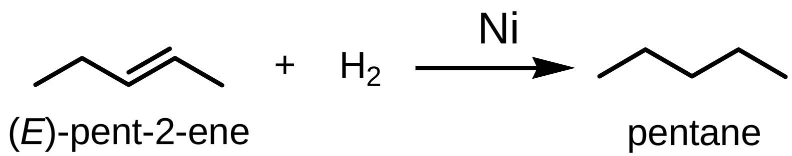


The Concept of Atom Economy

Addition

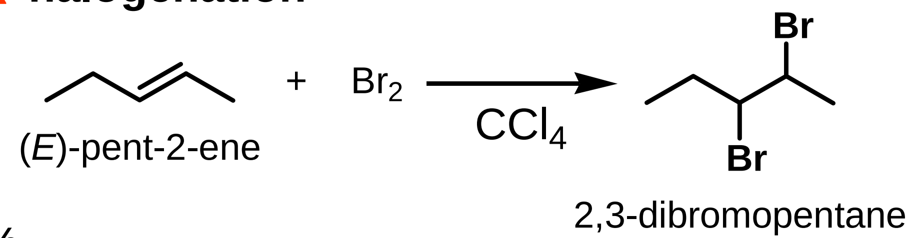
% atom economy = 100%

hydrogenation



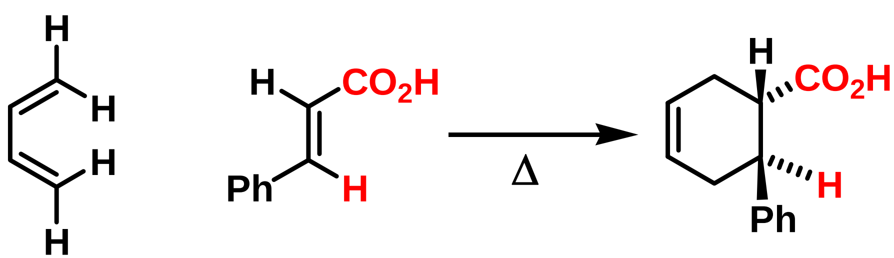
% atom economy = [72.15/(70.13 + 2.02)] x 100%
= 100%

halogenation

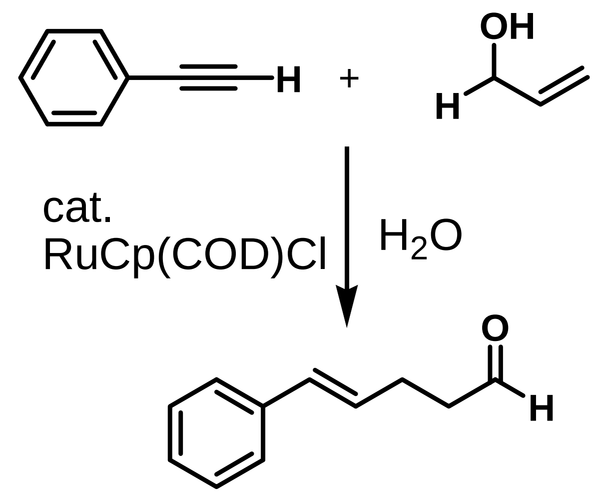


% atom economy = 100%

Diels-Alder reaction

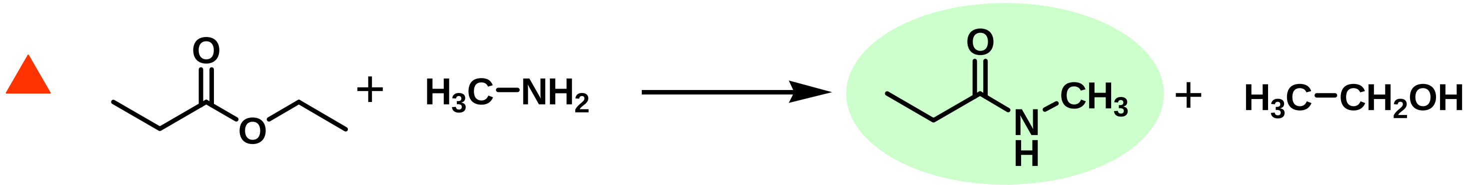


% atom economy = [202.25/(54.09 + 148.16)] x 100%
= 100%



Substitution

% atom economy < 100%



Reactants		Utilized		Unutilized	
Formula	*FW*	*Formula*	*FW*	*Formula*	*FW*
$C_5H_{10}O_2$	102.132	C_3H_5O	57.057	C_2H_5O	45.061
CH_3NH_2	31.057	CH_4N	30.049	H	1.008
$C_6H_{15}NO_2$	133.189	C_4H_9NO	87.106	C_2H_5OH	46.069

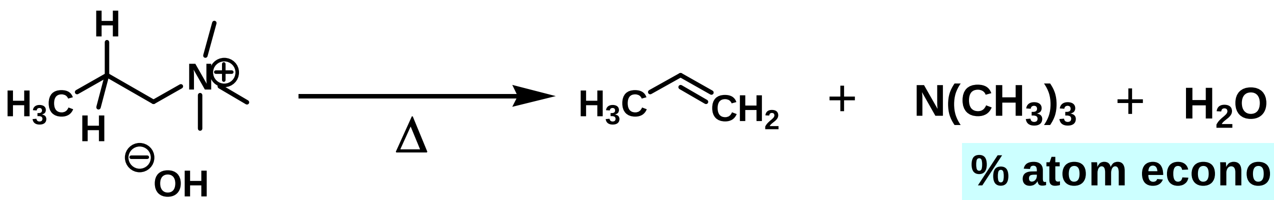
% atom economy = (87.106/133.189) x 100% = 65.4%

The Concept of Atom Economy

● *Elimination*

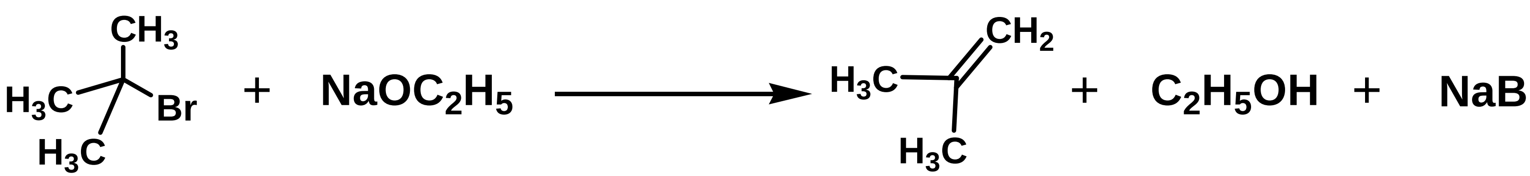
% atom economy < 100%

▲ **Hofmann elimination**



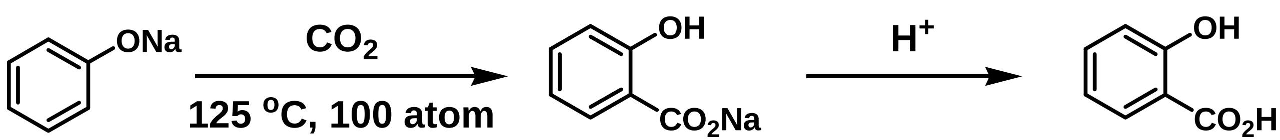
% atom economy = 35.30%

▲



% atom economy = 27%

✶ ✶



% atom economy = ?

sodium phenolate

sodium 2-hydroxybenzoate
sodium salicylate

2-hydroxybenzoic acid
salicylic acid

Kolbe-Schmitt reaction/Kolbe process

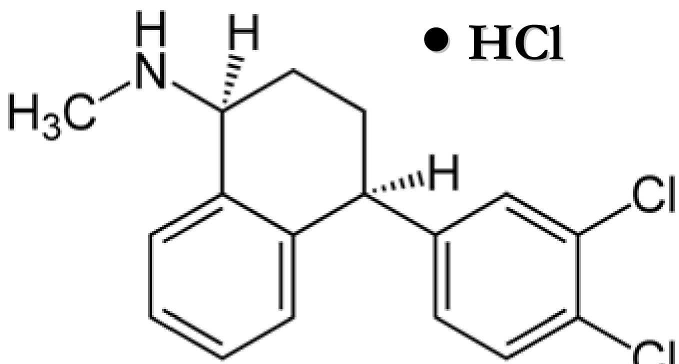
附錄三 (p.77~87)

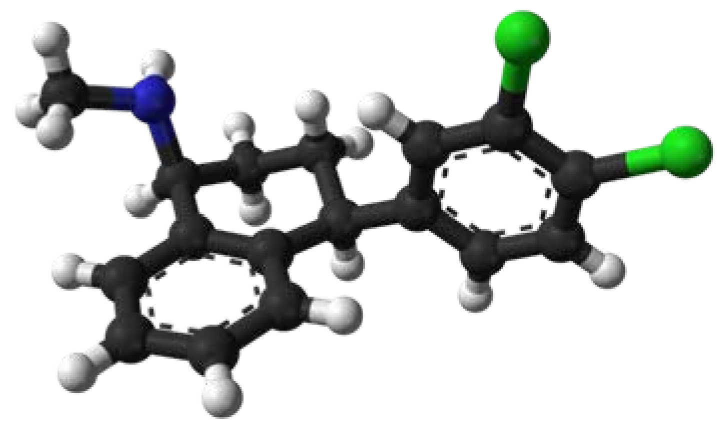
實例. Sertraline hydrochloride

報告於第一次
2010 永續合成化學工作坊
Feb 1, 2010, Taipei, TAIWAN

Case 2. 實例2

Sertraline hydrochloride



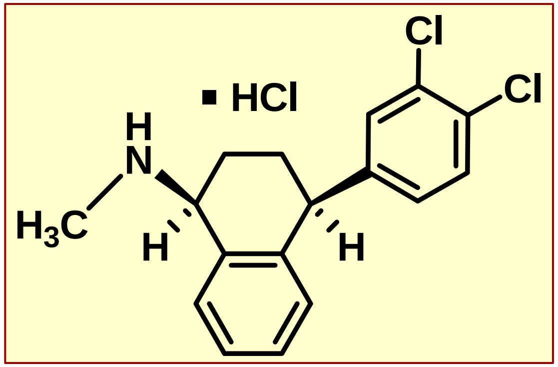


(1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine

What is Sertralin Hydrochloride?

精神科藥物Zoloft(樂復得)

- The empirical formula $C_{17}H_{17}NCl_2$•HCl is represented by the structural formula:



2 個掌心
4 個立體異構物
2 對鏡像異構物

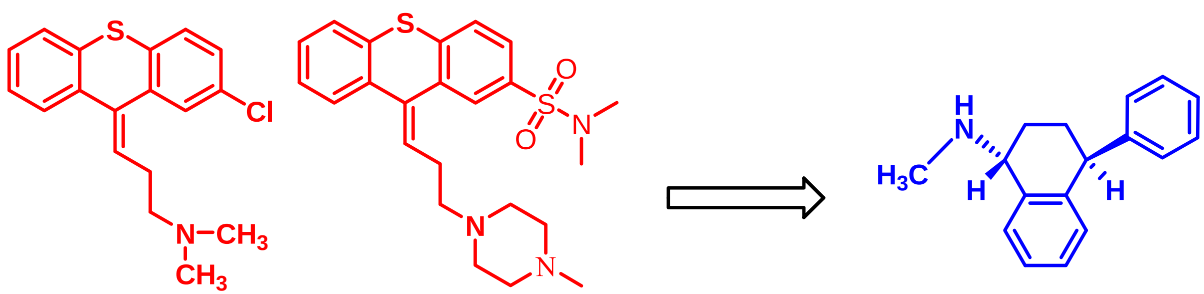
- Sertraline hydrochloride is a selective serotonin reuptake inhibitor (SSRI) (選擇性血清素再吸收抑制劑).

- It is an antidepressant（抗憂鬱症的）drug, used for treatment of major depression, panic disorder, obsessive-compulsive disorder, and posttraumatic stress disorder.
- It is sold by commercial name Zoloft® (Pfizer, Inc.).
- Approved for use in the U.S. in the early 1990s, it is the most prescribed drug of its class.
- It is used to treat an illness (depression) that each year strikes 20 million adults in the United States, and that costs society $43.7 billion (1990 dollars).
- As of February 2000, more than 115 million Zoloft® prescriptions had been written in the United States.

Sertraline hydrochloride

synthesis

- Early 1970s, Pfizer chemist Reinhard Sarges invented a novel series of psychoactive compounds based on the structures of neuroleptics chlorprothixene and thiothixene, leading to tametraline, a *norepinephrine* and weaker *dopamine reuptake inhibitor*.
- Development of tametraline was stopped because of undesired stimulant effects observed in animals.



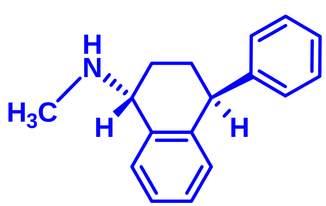
Chlorprothixene **Thiothixene** **Tametraline**

antipsychotic drugs

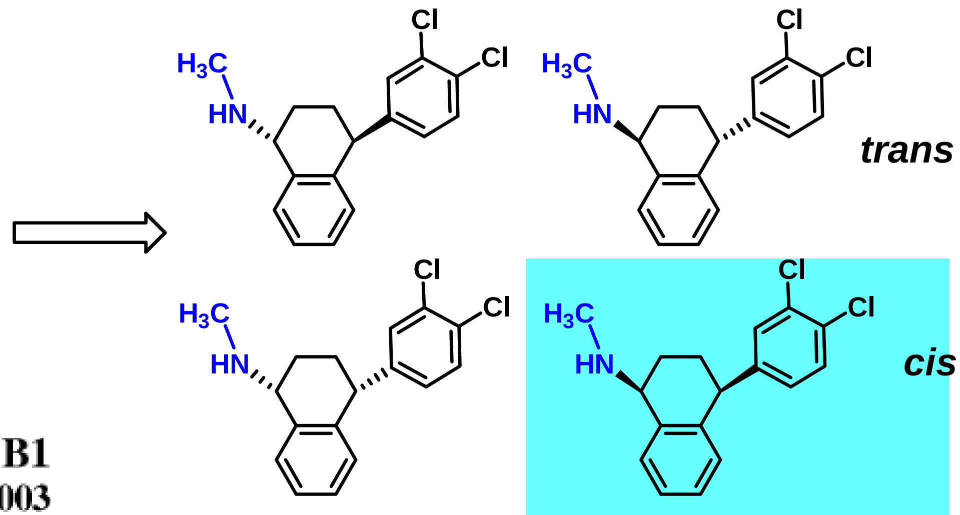
a norepinephrine and weaker dopamine reuptake inhibitor

* A norepinephrine reuptake inhibitor (NRI, NERI) or adrenergic reuptake inhibitor (ARI), is a type of drug which acts as a reuptake inhibitor for the neurotransmitters norepinephrine (noradrenaline) and epinephrine (adrenaline) by blocking the action of the norepinephrine transporter (NET).

- In 1977, pharmacologist K. Koe, after studying the structural features of a variety of reuptake inhibitors, became interested in the tametraline series.
- W. Welch was asked to synthesize some previously unexplored tametraline derivatives and found one representative of the generally inactive cis-analogs was a serotonin reuptake inhibitor.
- The most potent and selective (+)-isomer was taken into further development and eventually named sertraline--- an antidepressant of the SSRI type.
- The discovery of the sertraline molecule was *serendipitous*.



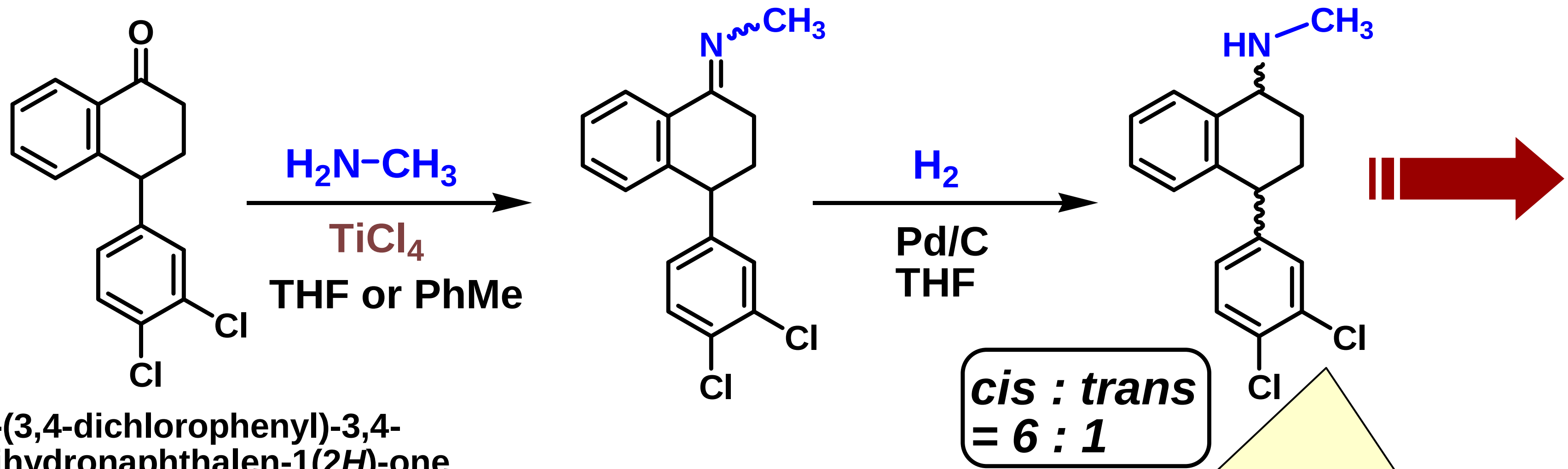
Tametraline



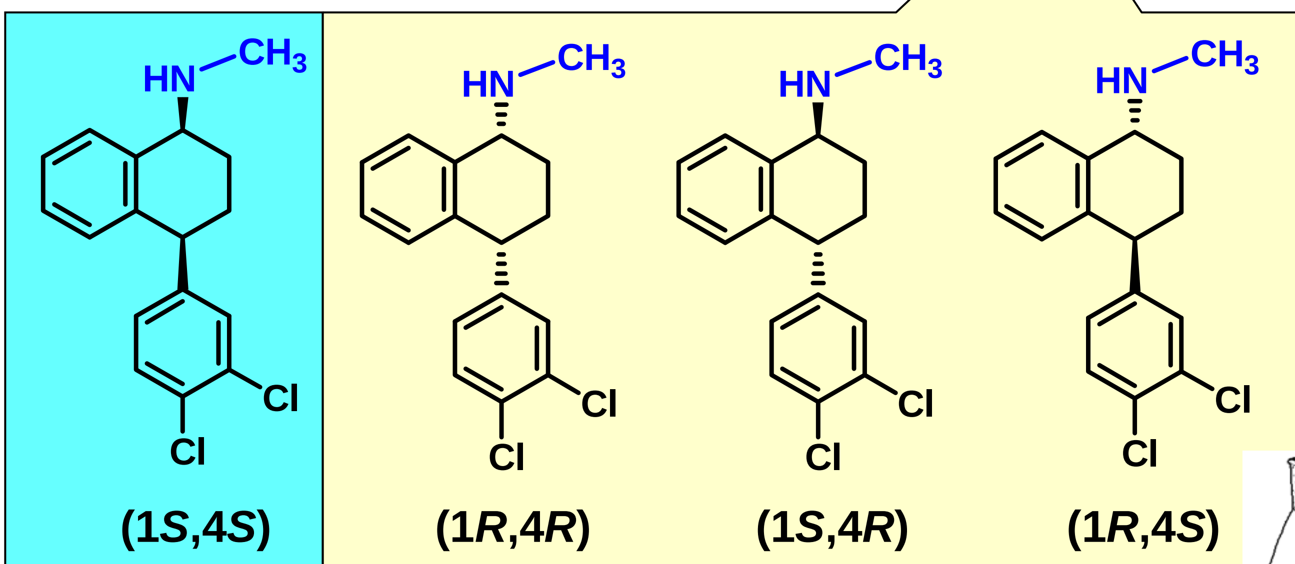
Patent No.: US 6,593,496 B1
Date of Patent: Jul. 15, 2003

Sertraline hydrochloride

The original three-step process



4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one

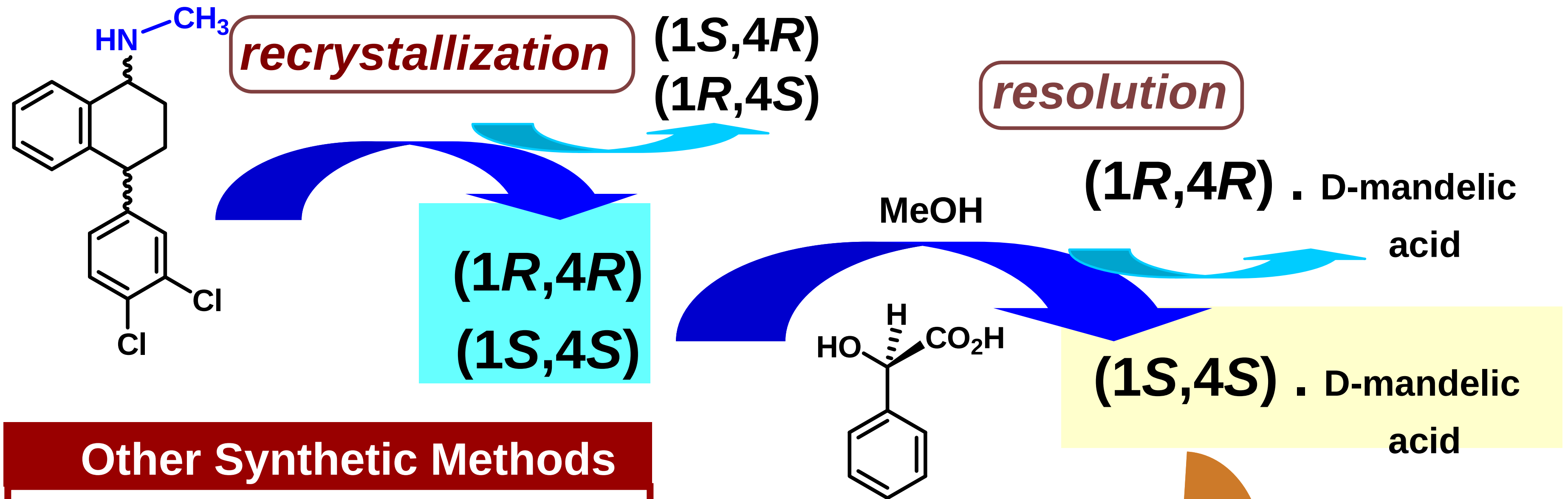


Sources

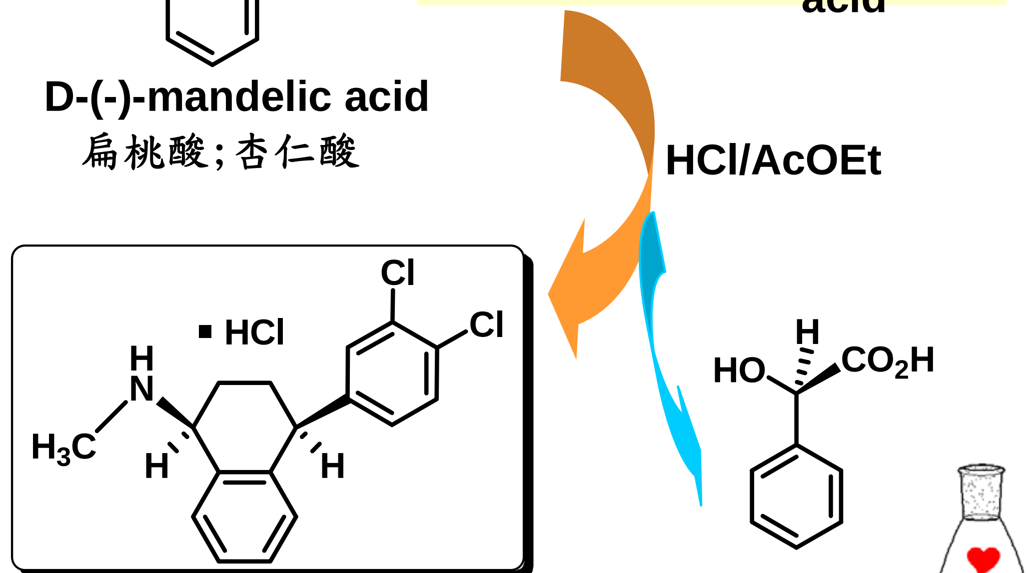
EP 0030081;
JP 1981086137;
US 6,232,500, 2001
Chem. Eng. News 2002, *80* (16), 30.
Org Proc Res Dev 2004, *8,* 385

Sertraline hydrochloride

Resolution Process



D-(-)-mandelic acid
扁桃酸;杏仁酸



Other Synthetic Methods

US 2003013768

US 2003013768

J Org Chem 2001, 66, 6988

Org Pro Res Dev 2002, 6, 82

Tetrahedron 2000, 56, 1111

Tetrahedron1999, 55, 8967

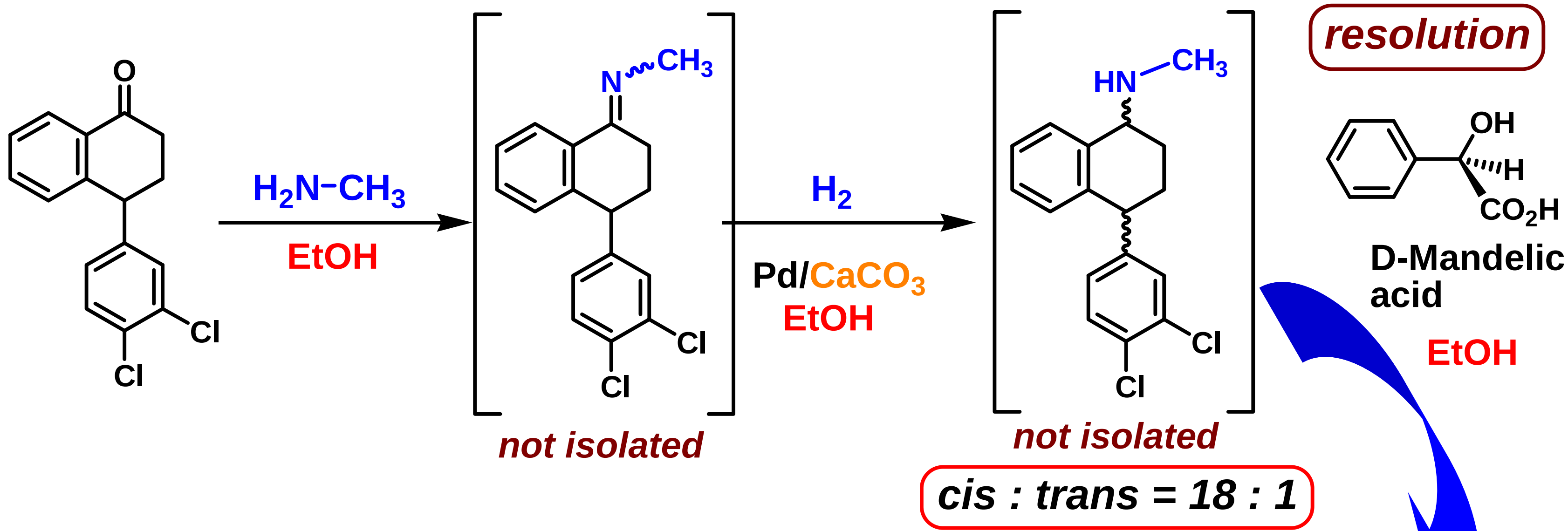
Drugs Fut 1984, 9, 277

Org Pro Res Dev 2008, 12, 168

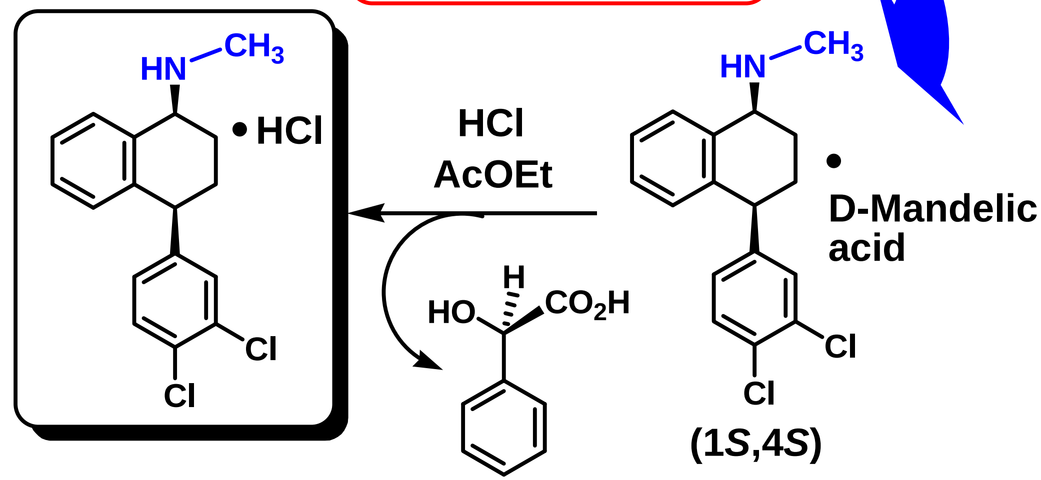
Org Pro Res Dev 2007, 11, 726

Sertraline hydrochloride

New Sertraline Process (Zoloft®, Pfizer)



- *developed by Pfizer process chemists G. Taber, J. Colberg, and D. Pfisterer.*



Sertraline hydrochloride

The “greener” features for the new sertraline process

- 3-step, 1-pot process without isolating intermediates.
- Introduction of EtOH as solvent.

  (→ reduce the solvent requirement from 60,000 to 6,000 gal/ton).
- Elimination of the need to use, distill, and recover four solvents (methylene chloride, tetrahydrofuran, toluene, and hexane).
- Elimination of using excess NH_2CH_3 (5 eq)

  (The imine formation is an equilibrium reaction; imine is sparingly soluble in EtOH, favoring equilibrium toward its formation → → cut down raw material used).

- Elimination of TiCl3 (used as dehydrating agent).
  (→ eliminating 440 tons of TiO_2, 150 tons 35% HCl, 100 tons 50% NaOH per year).
- Replacement of Pd/C with Pd/$CaCO_3$.
  (→ higher selectivity → → higher yield).
- Doubled the overall yield nearly to 37%.
  (→ cut raw materials by about 60, 45, and 20% for methylamine, dichlorophenyltetralone, and D-mandelic acid, respectively.)
- Reduction of energy and water use.
- Increases worker safety.

The 2002 US Presidential Green Chemistry Challenge Awards

in the category of

Greener Synthetic Pathways Award

Sertraline hydrochloride

附錄四 (p.88~101)

實例. The Cytovene® [ganciclovir]

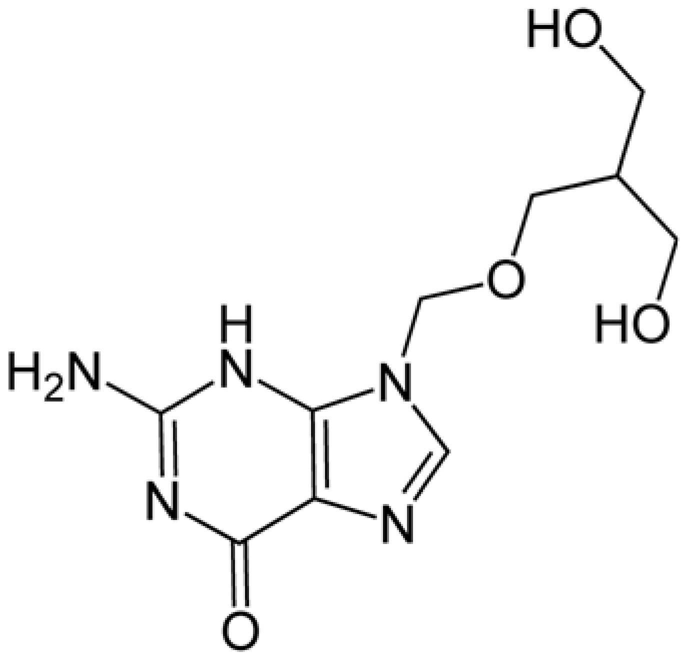
報告於第一次

2010 永續合成化學工作坊

Feb 1, 2010, Taipei, TAIWAN

Case 3. 實例3

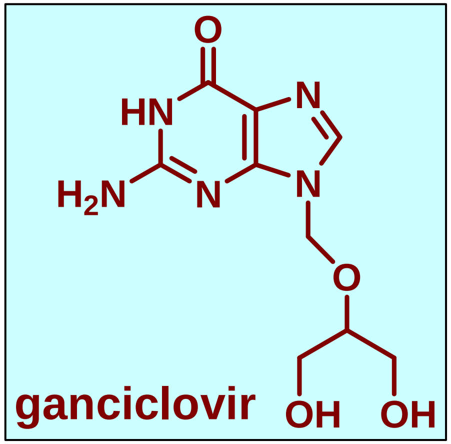
The Cytovene® [ganciclovir]



2-amino-9-{[(1,3-dihydroxypropan-2-yl)oxy]methyl}-6,9-dihydro-3*H*-purin-6-one

ganciclovir

What is ganciclovir [“更昔洛韋”]?

- 

Chemical Formula: $C_9H_{13}N_5O_4$
Exact Mass: 255.09675
Molecular Weight: 255.23062

IUPAC name:
2-amino-9-{[(1,3-dihydroxypropan-2-yl)oxy]methyl}-6,9-dihydro-3*H*-purin-6-one

- Ganciclovir is a prescription medication that belongs to the family of drugs known as “antivirals”.
[“更昔洛韋”是屬於抗病毒的處方藥劑]

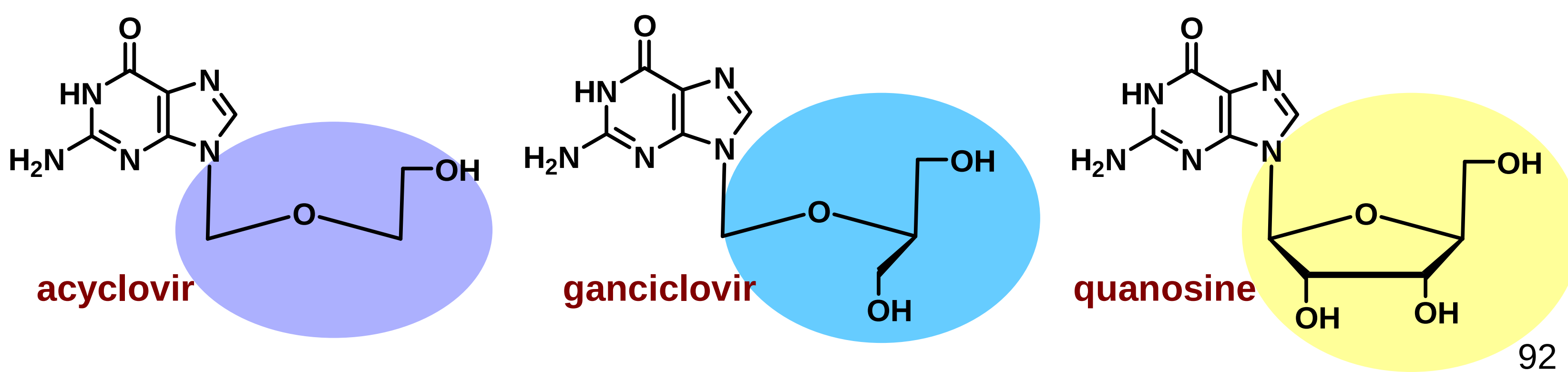
Cytovene (gancyclovir)

- Ganciclovir works by inhibiting cellular DNA polymerase that is associated with viral infections.
- Ganciclovir is used to treat for cytomegalovirus (CMV) retinitis infections in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS) or patients undergoing chemotherapy.
[“更昔洛韋”是用於治療免疫損害患者中的巨細胞病毒 (CMV) 視網膜炎，包括獲得性免疫缺陷綜合征（愛滋病）或化療病人。]
- Cytovene®, the registered trade name by the Roche Pharmaceuticals, contains ganciclovir sodium as the medicinal ingredient.

Cytovene (gancyclovir)

◆ synthesis

- In 1974, scientists at Wellcome discovered the potent antiviral agent acyclovir (Zovirax®) for the treatment of various viral infections including herpes viruses HSV-1 and HSV-2.
- In 1980, Dr. Kelvin Ogilvie and his research team at McGill University discovered Ganciclovir *[CAN. J. CHEM. 1982, 60, 3005.]*, and developed by Verheyden and Martin at Syntex Research in 1980.
- The first commercially viable process for the manufacture of ganciclovir was developed by Roche Colorado Corporation, formerly known as Syntex Chemicals, in the early 1990s.
- The 1st generation process is known as **Persilylation Process**.

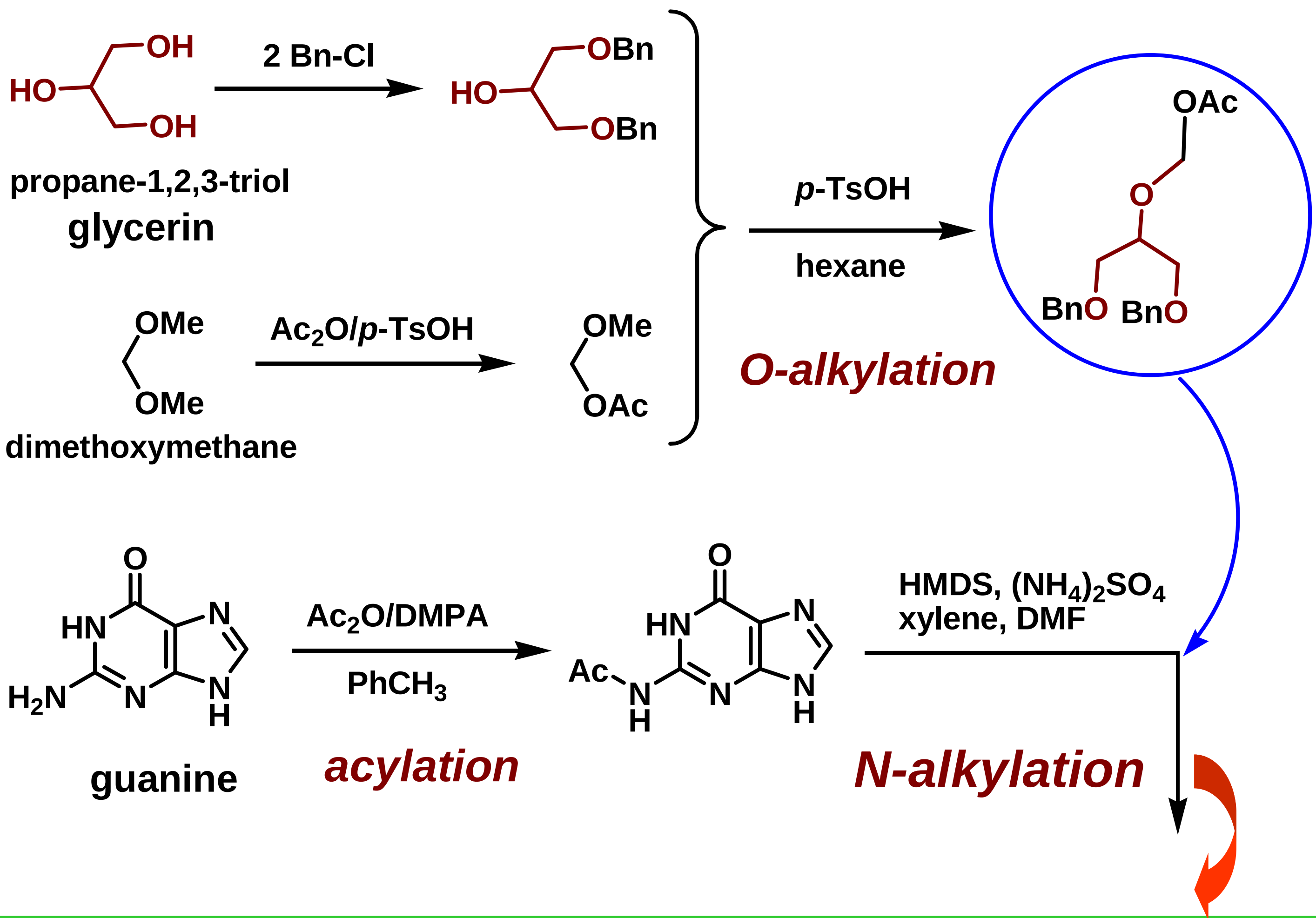


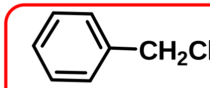
Cytovene (gancyclovir)

Persilylation Process --- Brown process

U.S. Patent 4, 621,140, November 4, 1986.

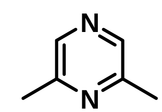
U.S. Patent 4,803,271, February 7, 1989.





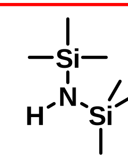
benzyl chloride

Bn-Cl



2,6-dimethylpyrazine

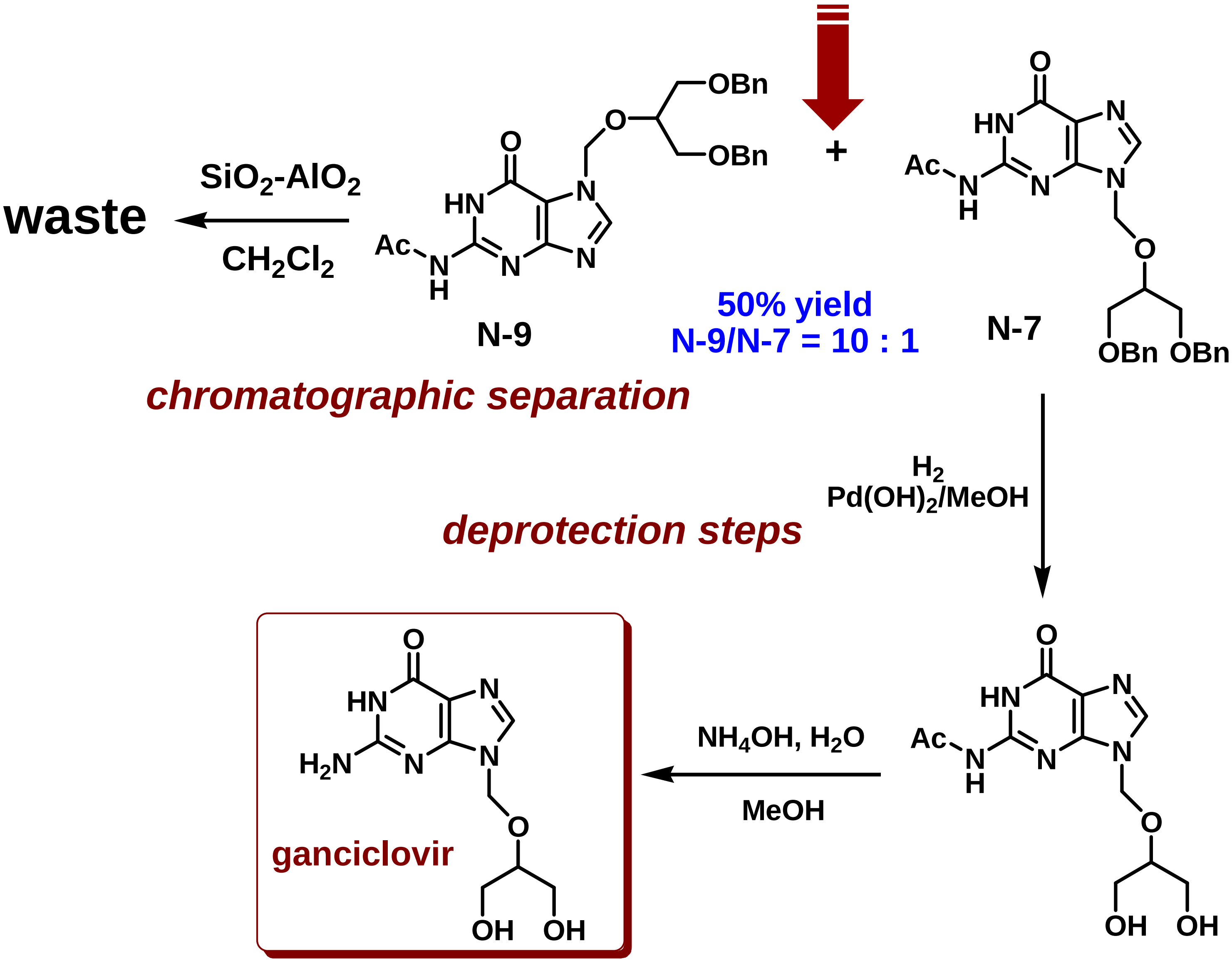
DMPA



Hexamethyl Disilazane

HMDS

Cytovene (gancyclovir)



Cytovene (gancyclovir)

Problems with Persilylation Process

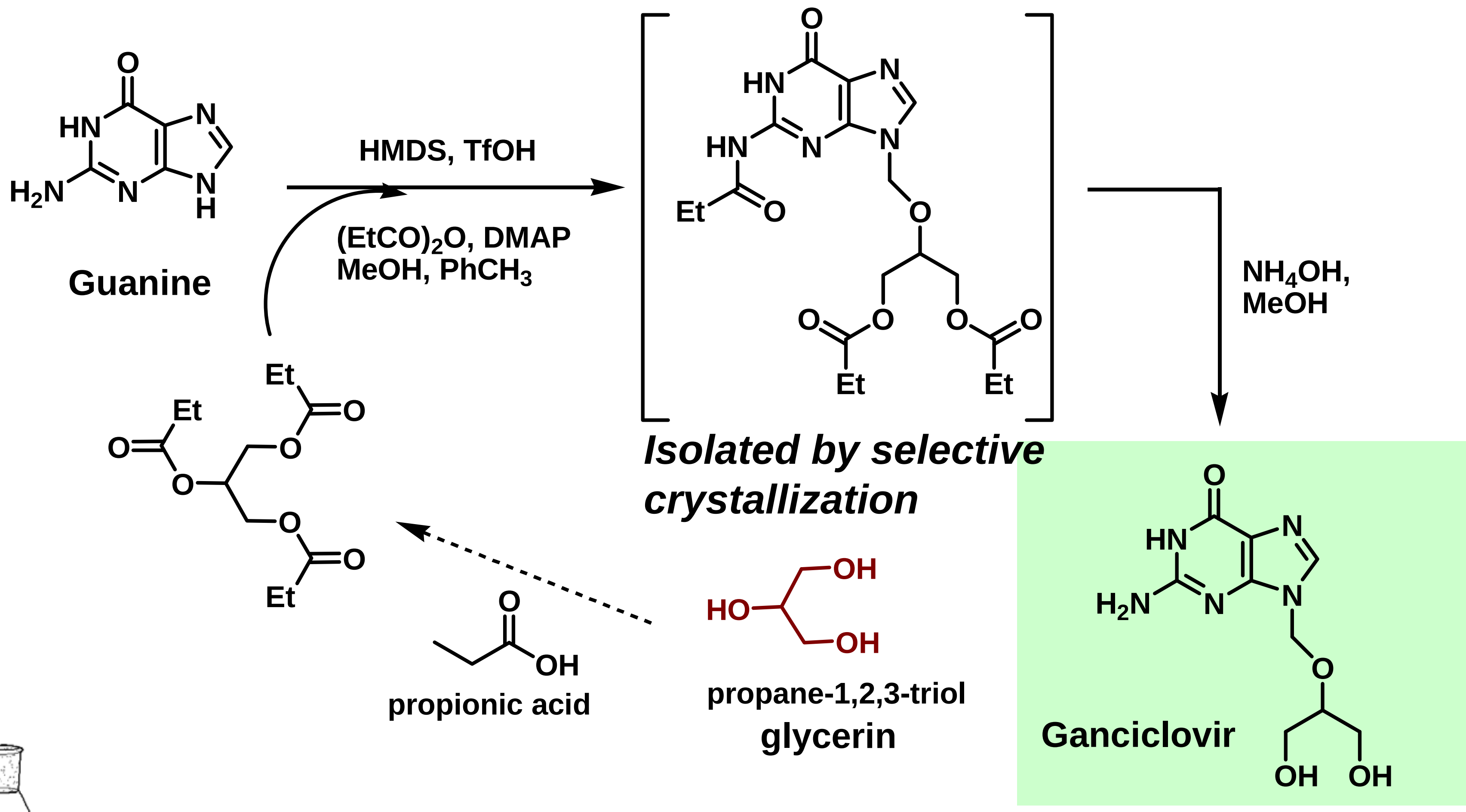
- A six-step process, in which 4-steps are protection-deprotection reactions.
- Involved 28 reagents and intermediates, and required the purification and isolation of 5 discrete intermediates.
- Involved at least 8 different kinds of solvents.
- Afforded specification grade ganciclovir in 54% yield.
- Involved a potentially hazardous palladium catalyzed hydrogenation step, which is needed to remove dibenzyl ether protecting group.
- Poor selectivity of key alkylation reaction, affording the desired N-7 isomer as minor product (N-7:N-9 = 1:10) and requiring costly and tedious chromatographic separation.

In 1993, the Boulder Technology Center of Roche Colorado Corporation completed the demonstration of a new and expedient process for the production of ganciclovir by (1) leveraging the **basic principles of molecular conservation** to minimize the creation and disposal of undesired wastes, and (2) formulating **efficient process engineering design** for streamlining process operation and the recycling of raw materials. The new (2nd generation) process is called

The Guanine TriEster (GTE) Process.

This technology was awarded the Presidential Green Chemistry Challenge Award [Greener Synthetic Pathways Award] in the U.S. in 2000.

The Guanine TriEster (GTE) Process
--- Green process



www.aspentech.com/publication_files/AICHE2000.pdf

Cytovene (gancyclovir)

The "greener" features of the GTE process

- **Fewer process steps:**
  - The process demonstrates the potential for a "one step" process for the production of ganciclovir.
- **Waste quantity reduction/elimination:**
  - Reduced the number of chemical reagents and intermediates from 28 to 11.
  - Eliminated 2 hazardous solid waste streams (SiO_2-AlO_2 & $Pd(OH)_2$).
  - Eliminated 11 different byproducts from the liquid waste streams.
  - Efficiently recycled and reused 4 of the 5 raw materials not incorporated into the final product.

[*U.S. Patent 5, 565, 565, October 15, 1996*.]

Cytovene (gancyclovir)

- Involved virtually no protection-deprotection steps, and thus eliminated a potentially hazardous palladium catalyzed hydrogenation step.
- The process thus reduced air emissions by ~66% and liquid/solid waste generation by ~89%.

- **Yield improved:**

  The process provides more than a 25% increase in overall yield and a 100% increase in production throughput.

- **Greener:**

  The process achieves applying the principles of

  1. Prevent Waste
  2. Increase Atom Economy
  3. Design Less Hazardous Chemical Syntheses

- The process designed and used a 4-carbon triester coupling reagent, which generated innocuous byproduct (EtCOOH) via simple hydrolysis.
- The process demonstrated the novel design of the direct silylation of guanine, that gives rise to a highly regioselective alkylation and thus less unwanted alkylated byproduct.

For a review of synthetic approaches to N-9 substituted guanies.

- F. P. Clausen and J. Juhl-Christensen, *Organic Prep. & Proced. Intl*., 1993, 25, 375.
- V. V. N. K. V. Prasada Raju, et. al. *ARKIVOC* 2009 (xii) 296-301.
- K. Izawa* and H. Shiragami, *Pure* & *Appl. Chem.,*1998, *70*, 313-318.

For the study describing a possible approach to selective alkylation of guanines.

- D. Sing, M.J. Wani and A. Kumar, *J. Org. Chem*. 1999, 64, 4664.
- J. Boryski and B. Golankiewicz, *Synthesis*, 1999, 625.
- United States Patent 7078524, Issued on July 18, 2006.

References

- Development of an Environmentally Friendly, Cost Effective Process for the Production of cytovene® Antiviral Agent. *www.aspentech.com/publication_files/AICHE2000.pdf*

- Biologically active acyclonucleoside analogues. 11. The synthesis of 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine (BIOLF-62). K. Ogilvieu, et. al., *Can. J. Chem*. **1982**, *60*, 3005.

- Synthesis of acyclovir, ganciclovir and their prodrugs: A review [Review], Gao, H.; Mitra, A. K. *Synthesis*, **2000**, 2000.

- Regioselective synthesis of various prodrugs of ganciclovir, Gao, H.; Mitra, A. K. *Tetrahedron Letters,* **2000**, *41*, 1131.

- A Facile Synthesis of 9-(1,3-Dihydroxy-2-propoxymethyl) guanine (Ganciclovir) from Guanosine, Boryski, et al., *Synthesis*, **1999**, 625.